

UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF VIRGINIA

WHOLE WOMAN'S HEALTH
ALLIANCE, *et al.*,

Plaintiffs,

v.

UNITED STATES FOOD AND DRUG
ADMINISTRATION, *et al.*,

Defendants.

Case No. 3:23-cv-00019-RSB

DECLARATION OF NOAH T. KATZEN

Pursuant to 28 U.S.C. § 1746, I, Noah T. Katzen, hereby declare:

1. I am an attorney in the Consumer Protection Branch of the U.S. Department of Justice, Civil Division. I am assigned to represent Defendants in the above-captioned case. The statements made herein are based on my personal knowledge, and on information made available to me in the course of my duties and responsibilities as Government counsel in this case.

2. I submit this declaration in support of Defendants' Combined Memorandum in Opposition to Plaintiffs' Motion for Preliminary Injunction and in Support of Motion to Stay Proceedings.

3. Filed herewith as Exhibits A – L are true and correct copies of the following documents that have been provided to me by the U.S. Food and Drug Administration or that I downloaded from the indicated websites:

EXHIBIT A



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020687/S-014

SUPPLEMENT APPROVAL

Danco Laboratories, LLC

(b) (6)

P.O. Box 4816
New York, NY 10185

Dear (b) (6):

Please refer to your Supplemental New Drug Application (sNDA) dated September 16, 2008, received September 17, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for MIFEPREX[®] (mifepristone) Tablets. We note that NDA 020687 is approved under the provisions of 21 CFR 314.520 (Subpart H).

This supplemental application provides for a proposed risk evaluation and mitigation strategy (REMS) for MIFEPREX (mifepristone) and was submitted in accordance with section 909(b)(1) of the Food and Drug Administration Amendments Act of 2007 (FDAAA). Under section 909(b)(1) of FDAAA, we identified MIFEPREX (mifepristone) as a product deemed to have in effect an approved REMS because there were in effect on the effective date of FDAAA, March 25, 2008, elements to assure safe use required under 21 CFR 314.520.

We acknowledge receipt of your amendments dated December 9, 2008, November 8, 2010, and May 19 and 27, 2011.

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for MIFEPREX (mifepristone) to ensure the benefits of the drug outweigh the risks of serious complications by requiring prescribers to certify that they are qualified to prescribe MIFEPREX (mifepristone) and are able to assure patient access to appropriate medical facilities to manage any complications.

Your proposed REMS, as amended and appended to this letter, is approved. The REMS consists of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

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The REMS assessment plan will include the information submitted to FDA on May 27, 2011, and should include the following information:

- a. Per section 505-1(g)(3)(A), an assessment of the extent to which the elements to assure safe use are meeting the goal or goals to mitigate a specific serious risk listed in the labeling of the drug, or whether the goal or goals or such elements should be modified.
- b. Per section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such postapproval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such postapproval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in Section 505-1(g)(2)(A) of FDCA.

Prominently identify future submissions containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

NDA 020687 REMS ASSESSMENT

**NEW SUPPLEMENT FOR NDA 020687
PROPOSED REMS MODIFICATION
REMS ASSESSMENT**

**NEW SUPPLEMENT (NEW INDICATION FOR USE) FOR NDA 020687
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)**

If you do not submit electronically, please send 5 copies of REMS-related submissions.

As part of the approval under Subpart H, as required by 21 CFR 314.550, you must submit all promotional materials, including promotional labeling as well as advertisements, at least 30 days

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before the intended time of initial distribution of the labeling or initial publication of the advertisement. Send one copy to the [REDACTED] (b) (6) and two copies of the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, [REDACTED] (b) (6)

Sincerely,

{See appended electronic signature page}

[REDACTED] (b) (6)

ENCLOSURES:

REMS Document
REMS Materials

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

(b) (6)

06/08/2011

EXHIBIT B



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020687/S-022

SUPPLEMENT APPROVAL

Danco Laboratories, LLC
(b) (4), (b) (6)

P.O. Box 4816
New York, NY 10185

Dear (b) (4), (b) (6) :

Please refer to your Supplemental New Drug Application (sNDA) dated November 4, 2015, received November 5, 2015, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Mifeprex (mifepristone) Tablets.

This Prior Approval supplemental new drug application proposes modifications to the approved risk evaluation and mitigation strategy (REMS) for Mifeprex to establish a single, shared system (SSS) REMS for mifepristone products for the medical termination of intrauterine pregnancy and updates to the approved Prescribing Information, Medication Guide, and REMS materials including the Prescriber Agreement and Patient Agreement Forms to incorporate language reflecting the proposed SSS REMS.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at:

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<http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Mifeprex (mifepristone) Tablets was originally approved on June 8, 2011. The most recent modification was approved on March 29, 2016. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS establish a SSS REMS for the elements to assure safe use and the implementation system required for the reference listed drug (RLD) Mifeprex and ANDAs referencing Mifeprex, called the Mifepristone REMS Program.

Your proposed modified REMS, submitted on January 25, 2018, and appended to this letter, is approved.

The timetable for submission of assessments of the REMS must be revised to one year from the date of the initial approval of the SSS REMS (04/11/19) and every three years thereafter.

The revised REMS assessment plan must include, but is not limited to, the following:

Both cumulative data from the date of the initial approval of the SSS REMS (04/11/19) and data from the reporting period (i.e., from the preceding Mifeprex REMS assessment cut-off date to the cut-off date for the Mifepristone REMS Program.)

REMS Assessment Plan

Provide each metric for the current reporting period and cumulative for the RLD and ANDA(s):

1. Number of prescribers enrolled
2. Number of prescribers ordering mifepristone
3. Number of healthcare providers who attempted to order mifepristone who were not enrolled; describe actions taken
4. Number of women exposed to mifepristone
5. Summary and analysis of any program deviations and corrective action taken
6. Based on the information reported, an assessment and analysis of whether the REMS is meeting its goals and whether modifications to the REMS are needed

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or such elements should be modified.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support any proposed REMS modification for the addition, modification, or removal of any of goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit any future supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

- a) An evaluation of how the benefit-risk profile will or will not change with the new indication;
- b) A determination of the implications of a change in the benefit-risk profile for the current REMS;
- c) *If the new indication for use introduces unexpected risks:* A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.
- d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* A statement about whether the REMS was meeting its goals at the time of that the last assessment and if any modifications of the REMS have been proposed since that assessment.
- e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.
- f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including:* Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications, provide a rationale for why the REMS does not need to be modified.*

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous

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REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 020687 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT
METHODOLOGY**

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 020687 REMS ASSESSMENT

**NEW SUPPLEMENT FOR NDA 020687/S-000/ SECONDARY TRACKING
NUMBER
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION**

Or

**NEW SUPPLEMENT FOR NDA 020687/S-000/ SECONDARY TRACKING
NUMBER
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL
CHANGES SUBMITTED IN SUPPLEMENT XXX**

Or

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 020687/S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)**

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page

NDA 020687/S-022
Page 5

of the submission:

REMS REVISIONS FOR NDA 020687

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, as soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in SPL format using the FDA automated drug registration and listing system (eLIST).

For more information on submitting REMS in SPL format, please email REMS_Website@fda.hhs.gov.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call

(b) (6)

Sincerely,

{See appended electronic signature page}

(b) (6)

Center for Drug Evaluation and Research

NDA 020687/S-022

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ENCLOSURES:

Content of Labeling

Prescribing Information

Medication Guide

REMS

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

(b) (6)

04/11/2019 02:13:59 PM

EXHIBIT C

Center for Drug Evaluation and Research (CDER)
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Application Type NDA and ANDA
Application Number 020687 and 91178
Reviewer Names (b) (6), (b) (6)
(b) (6)
(b) (6), (b) (6) (b) (6)

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Review Completion Date December 16, 2021

Subject	REMS Modification Rationale Review
Established Name	Mifepristone REMS
Name of Applicants	Danco Laboratories, LLC and GenBioPro, Inc.
Therapeutic Class	Progestin antagonist
Formulation	Oral tablets

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EXECUTIVE SUMMARY

This review provides the (b) (6) (b) (6) and (b) (6) (b) (6) rationale and conclusions regarding modifications to the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone 200 mg (Mifepristone REMS Program) for new drug application (NDA) 20687 and abbreviated new drug application (ANDA) 91178.

ANDA 91178 was approved with the approval of the Mifepristone REMS Program on April 11, 2019 to mitigate the risk of serious complications associated with mifepristone 200 mg. The most recent REMS modification was approved on May 14, 2021. The REMS consists of elements to assure safe use (ETASU) under ETASU A, C and D, an implementation system, and a timetable for submission of assessments. To determine whether a modification to the REMS was warranted, FDA undertook a comprehensive review of the published literature; safety information collected during the COVID-19 public health emergency (PHE); the one-year REMS assessment report of the Mifepristone REMS Program; adverse event data; and information provided by advocacy groups, individuals and the Applicants. Our review also included an examination of literature references provided by plaintiffs in the *Chelius v. Becerra* litigation discussed below.

The modifications to the REMS will consist of:

- Removing the requirement under ETASU C that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (referred to here as the “in-person dispensing requirement” for brevity)
- Adding a requirement under ETASU B that pharmacies that dispense the drug be specially certified

A REMS Modification Notification letter will be sent to both Applicants in the Single Shared System.

1. Introduction

In connection with the *Chelius v. Becerra* litigation, FDA agreed to undertake a full review of the Mifepristone REMS Program, in accordance with the REMS assessment provisions of the Federal Food, Drug, and Cosmetic Act (FD&C Act).^a This review provides the analysis of the

(b) (6) (b) (6) and the (b) (6) (b) (6) regarding whether any changes are warranted to the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone (hereafter referred to as the Mifepristone REMS Program) for new drug application (NDA) 20687 and abbreviated new drug application (ANDA) 91178. The Mifeprex REMS was initially approved in 2011; the single, shared system REMS for mifepristone 200 mg, known as the Mifepristone REMS Program, was approved in 2019.

The last time the existing REMS elements to assure safe use (under ETASU A, C and D) were reviewed was in the context of our review of supplement S-020 to NDA 20687; these ETASU were updated following review and approval of supplement S-020 on March 29, 2016. The key changes approved in 2016 are summarized below.

Changes to labeling included:

- Changing the dosing of Mifeprex to 200 mg orally x 1
- Extension of maximum gestational age through 70 days
- Inclusion of misoprostol in the indication statement
- Replacing the term “physician” with “licensed healthcare provider”
- Removal of the phrase “Under Federal Law”

The Mifeprex REMS and REMS materials were updated to reflect the changes above, and additional changes were made including:

- Removing the Medication Guide as part of the REMS but retaining it as part of labeling.

2. Background

2.1. PRODUCT AND REMS INFORMATION

^a Section 505-1(g)(2) of the FD&C Act (21 U.S.C. § 355-1(g)(2)).

Mifepristone is a progestin antagonist indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy (IUP) through 70 days gestation. Mifepristone is available as 200 mg tablets for oral use.

Mifeprex (mifepristone) was approved on September 28, 2000 with a restricted distribution program under 21 CFR 314.520 (subpart H)^b to ensure that the benefits of the drug outweighed the risk of serious complications associated with mifepristone when used for medical abortion. Mifeprex was deemed to have a REMS under section 505-1 of the Federal Food, Drug, and Cosmetic Act with the passage of the Food and Drug Administration Amendments Act (FDAAA) of 2007, and the Mifeprex REMS was approved on June 8, 2011. On March 29, 2016, as noted above, a supplemental application and REMS modification was approved for Mifeprex. On April 11, 2019, ANDA 091178 was approved, and the Mifepristone REMS Program was approved. The Mifepristone REMS Program is a single, shared system REMS that includes NDA 020687 and ANDA 91178.

The goal of the REMS for mifepristone is to mitigate the risk of serious complications associated with mifepristone by:

- a. Requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program (under ETASU A).
- b. Ensuring that mifepristone is only dispensed in certain healthcare settings, by or under the supervision of a certified prescriber (under ETASU C).
- c. Informing patients about the risk of serious complications associated with mifepristone (under ETASU D).

Under ETASU A, to become specially certified to prescribe mifepristone, a healthcare provider must review the prescribing information, complete and sign the *Prescriber Agreement Form*, and follow the guidelines for use of mifepristone. Under ETASU C, mifepristone must be dispensed to patients only in certain healthcare settings, specifically clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber. Under ETASU D, mifepristone must be dispensed to patients with evidence or other documentation of safe use conditions (i.e., the patient must sign a *Patient Agreement Form*). The Mifepristone REMS Program also includes an implementation system, and a timetable for assessments (one year from the date of the initial approval of the REMS on April 11, 2019, and every three years thereafter).

^b NDA approval letter Mifeprex (NDA 020687) dated September 28, 2000.

2.2. REGULATORY HISTORY AND EVENTS RELEVANT TO THIS REMS MODIFICATION RATIONALE REVIEW

The following is a summary of significant regulatory history since approval of the REMS modification on March 29, 2016:

- 03/29/2016: FDA approved an efficacy supplement (S-020) that, among other things, provided a new dosing regimen (200 mg mifepristone, followed in 24 to 48 hours by 800 mcg buccal misoprostol), increased the gestational age (GA) to which mifepristone may be used (through 70 days gestation), and modified the REMS.
- 03/29/2019: A Citizen Petition was received requesting that FDA revise the product labeling to reflect pre-2016 provisions (including limiting GA to 49 days and requiring patients to make 3 office visits) and that FDA maintain the REMS.
- 04/11/2019: ANDA 91178 was approved along with the Single Shared System REMS for Mifepristone 200 mg (Mifepristone REMS Program) for NDA 20687 and ANDA 91178.
- 01/31/2020: the COVID-19 public health emergency (PHE) was declared by the Secretary of Health and Human Services (HHS) as having existed since January 27, 2020.^c
- 7/13/2020: The United States (US) District Court of Maryland granted a preliminary injunction in the *ACOG v. FDA* litigation to temporarily bar enforcement of the Mifepristone REMS Program in-person dispensing requirement during the COVID-19 PHE.
- 1/12/2021: US Supreme Court granted a stay of that injunction.
- 04/12/2021: FDA issued a General Advice Letter to both the NDA and ANDA Applicants, stating that provided that all other requirements of the Mifepristone REMS Program are met, and given that in-person dispensing of mifepristone for medical termination of early pregnancy may present additional COVID-related risks to patients and healthcare

^c See Secretary of Health and Human Services, Determination that a Public Health Emergency Exists (originally issued January 31, 2020, and subsequently renewed), available at <https://www.phe.gov/emergency/news/healthactions/phe/Pages/default.aspx>

personnel because it may involve a clinical visit solely for this purpose, FDA intends to exercise enforcement discretion during the COVID-19 PHE with respect to the in-person dispensing requirement in the Mifepristone REMS Program, including any in-person requirements that may be related to the *Patient Agreement Form*. FDA further stated that to the extent all of the other requirements of the Mifepristone REMS Program are met, FDA intends to exercise enforcement discretion during the COVID-19 PHE with respect to the dispensing of mifepristone through the mail, either by or under the supervision of a certified prescriber, or through a mail-order pharmacy when such dispensing is done under the supervision of a certified prescriber.

- 05/07/2021: FDA stated that it would be reviewing the elements of the Mifepristone REMS Program in accordance with the REMS assessment provisions of section 505-1 of the FD&C Act.
- 05/14/2021: A modification was approved for the Mifepristone REMS Program. This modification was to revise the *Patient Agreement Form* to include gender-neutral language.
- 06/30/2021: An Information Request (IR) was sent to the Applicants for additional information on shipments and any program deviations, adverse events, or noncompliance with the REMS that occurred during the period from April 1, 2021 through September 30, 2021.
- 7/15/2021: An IR was sent to the Applicants to provide the total number of shipments during the period from April 1, 2021 to September 30, 2021 and details on whether any of those shipments were involved in any program deviation or non-compliance.
- 8/5/2021: An IR was sent to the Applicants for additional clinical and other information (e.g., adverse events and units of mifepristone shipped) for the period of March 29, 2016 through June 30, 2021, to be provided by August 31, 2021. This IR also requested information covering the period of July 1, 2021 through September 30, 2021 and an

aggregate summary (for the period of March 29, 2016 through September 30, 2021), to be provided by October 12, 2021.^d

- 8/26/2021: The ANDA Applicant submitted a response to the IR issued on 8/5/2021.
- 08/27/2021: The NDA Applicant submitted a response to the IR issued on 8/5/2021.
- 10/08/2021: The NDA Applicant submitted a response to the June 30 and July 15, 2021 IRs as well as an aggregate summary for the period March 29, 2016 through September 30, 2021 in response to the August 5, 2021 IR. The NDA Applicant also included a follow-up to their initial response provided on August 27, 2021 to the August 5, 2021 IR.
- 10/12/2021: The ANDA Applicant submitted a response to the June 30 and July 15, 2021 IRs as well as an aggregate summary for the period March 29, 2016 through September 30, 2021 in response to the August 5, 2021 IR.
- 10/16/2021: The ANDA Applicant revised their Oct 12, 2012 response to provide a correction to the number of mifepristone tablets.
- [REDACTED] (b) (4)
[REDACTED] .
- 11/02/2021: A [REDACTED] (b) (6) ([REDACTED] (b) (6)) meeting was convened to obtain CDER concurrence on the removal of the in-person dispensing requirement and the addition of a certification requirement for pharmacies. The [REDACTED] (b) (6) [REDACTED] (b) (6) and senior CDER leadership concurred with removing the in-person dispensing and adding pharmacy certification.

3. Rationale for Proposed REMS Modification

^d Multiple Information Requests were issued to obtain additional information on drug shipments, any program deviations or noncompliance, and use of alternative methods for drug distribution during the COVID-19 PHE. These IRs are referenced as appropriate in this document and the one-year REMS Assessment Review of the Mifepristone REMS Program, December 16, 2021.

3.1. CURRENT REQUIREMENTS FOR THE APPROVED REMS

The Mifepristone REMS Program includes elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments. Elements to assure safe use in the current REMS include a prescriber certification requirement (ETASU A), a requirement that mifepristone be dispensed only in certain healthcare settings by or under the supervision of a certified prescriber (ETASU C), and a requirement that mifepristone be dispensed only with documentation of safe use conditions (ETASU D). Documentation of safe use conditions under ETASU D consists of a *Patient Agreement Form* between the prescriber and the patient indicating that the patient has received counseling from the prescriber regarding the risk of serious complications associated with mifepristone 200 mg for medical termination of early pregnancy.

3.2. EVALUATION OF THE EVIDENCE

We reviewed multiple different sources of information, including published literature, safety information submitted to the Agency during the COVID-19 PHE, FDA Adverse Event Reporting System (FAERS) reports, the first REMS assessment report for the Mifepristone REMS Program, and information provided by advocacy groups, individuals, and the Applicants. Our review also included an examination of literature references provided by plaintiffs in the *Chelius v. Becerra* litigation. Below is an overview of how information relevant to the current Mifepristone REMS Program was retrieved, analyzed, and applied to each of the individual ETASUs to determine if further changes should be considered.

Methods for the literature search

(b) (6) conducted a literature search in PubMed and Embase to retrieve publications relevant to this review. The time period used for this literature search was between March 29, 2016 (when the Mifeprex labeling and REMS were last substantially revised) through July 26, 2021. The search terms used were “medical abortion” and “mifepristone” and “pregnancy termination and mifepristone.”

The search retrieved 306 publications from PubMed and 613 from Embase, respectively; the search yielded 646 unique publications after eliminating duplications between the two databases. The result of our literature search was also supplemented by an examination of literature references provided by advocacy groups, individuals, plaintiffs in the *Chelius* litigation, and the Applicants, as well as letters from healthcare providers and researchers.

References included in these letters were considered for inclusion in this review using identical selection criteria to the (b) (6) literature search (outlined below).

For this review of the REMS, (b) (6) focused on publications containing safety data related to outcomes of medical abortion (objective safety data) obtained from our literature search and from the references provided to us relevant to the REMS ETASUs. We excluded systematic reviews and meta-analyses because these publications did not include original safety data related to the outcomes of medical abortion. The following are examples of materials that were excluded from our literature search:

- Information from survey studies or qualitative studies that evaluated perspectives on and/or satisfaction with medical abortion procedures from patients, pharmacists, clinic staff, or providers, even if the study assessed REMS ETASUs. These surveys or qualitative studies did not include objective safety data related to outcomes of medical abortion.
- Opinions, commentaries, or policy/advocacy statements. These publications did not include objective safety data related to outcomes of medical abortion.
- Safety data related to mifepristone use for second trimester medical abortion. These publications reported data not applicable to the approved indication for medical abortion up to 70 days gestation.
- Safety data related to mifepristone use for spontaneous first trimester abortion (i.e., miscarriages). These publications reported data not applicable to the approved indication for medical abortion up to 70 days gestation.
- Safety data that pertained only to surgical abortion or did not separate out medical abortion from surgical abortion.
- Other safety information unrelated to the REMS elements (e.g., articles limited to case reports or those discussing unrelated gynecologic or medical issues)
- Publications for which it was not possible to conduct a full review of the methods or results, i.e., the references were limited to an abstract of the study methods and results.
- Publications that provided only general statistics on abortion care in the United States.

- Information pertinent to molecular or other basic science aspects of mifepristone.
- Data on the logistics of accessing abortion care in general, such as time to appointment or the distance traveled to obtain care.
- Publications that provided data not related specifically to abortion care or the REMS (e.g., references focused on federal poverty guidelines, poverty data, or the financial impact of the COVID-19 pandemic).

One exception to the above literature search criteria was the inclusion in Section 3.2.2 of this review, which discusses the *Patient Agreement Form*, of publications that discussed changes in provider volume. The data discussed in relation to provider volume was obtained from surveys. This data was included because changes in provider volume could only be obtained from well-conducted survey studies.

Regarding medical/scientific references submitted with letters from the plaintiffs in the *Chelius* litigation, we applied the same criteria as for the literature search, as described above.

Letters from the plaintiffs in the *Chelius* litigation included several references that preceded our 2016 review of the REMS. Two of those pre-2016 studies were not captured in our 2016 literature search. These two studies were assessed as part of our current review; their results are consistent with the existing safety profile of the approved medical abortion regimen, and therefore, support our current conclusions regarding the REMS. See Appendix A.

3.2.1. Evaluation of the requirement for healthcare providers who prescribe the drug to be specially certified (ETASU A)

In order to become specially certified, prescribers must: 1) review the prescribing information for mifepristone and 2) complete the *Prescriber Agreement Form*. In signing the *Prescriber Agreement Form*, prescribers agree they meet the qualifications listed below:

- Ability to assess the duration of pregnancy accurately
- Ability to diagnose ectopic pregnancies
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or to have made plans to provide such care through others, and ability to

ensure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.

- Has read and understood the Prescribing Information of mifepristone (which the provider can access by phone or online).

In addition to meeting these qualifications, as a condition of certification the healthcare provider also agrees to follow the guidelines for use below:

- Review the *Patient Agreement Form* with the patient and fully explain the risks of the mifepristone treatment regimen. Answer any questions the patient may have prior to receiving mifepristone.
- Sign and obtain the patient's signature on the *Patient Agreement Form*.
- Provide the patient with a copy of the *Patient Agreement Form* and the Medication Guide.
- Place the signed *Patient Agreement Form* in the patient's medical record.
- Record the serial number from each package of mifepristone in each patient's record.
- Report deaths to the Applicant, identifying the patient by a non-identifiable patient reference and the serial number from each package of mifepristone.

The literature review was the primary source of information that contributed to our reassessment of ETASU A.

We continue to be concerned that absent these provider qualifications, serious and potentially fatal complications associated with medical abortion, including missed ectopic pregnancy and heavy bleeding from incomplete abortion, would not be detected or appropriately managed. Our review of the literature did not identify any studies comparing providers who met these qualifications with providers who did not. In the absence of such studies, there is no evidence to contradict our previous finding that prescribers' ability to accurately date pregnancies, diagnose ectopic pregnancies, and provide surgical intervention or arrange for such care through others if needed, is necessary to mitigate the serious risks associated with the use of mifepristone in a regimen with misoprostol. Therefore, our review continues to support the conclusion that a healthcare provider who prescribes mifepristone should meet the above qualifications. We conclude it is reasonable to maintain the requirement for a one-time prescriber certification where prescribers attest to having the ability to diagnose an intrauterine

pregnancy, to diagnose an ectopic pregnancy,^e and to either manage serious complications themselves or arrange for other providers to provide the needed care in a timely manner.

In addition, in signing the *Prescriber Agreement Form* and placing it in the patient's medical record, the prescribers acknowledge the requirement to report patient deaths associated with mifepristone to the manufacturer. Such a requirement ensures that the manufacturer receives all reports of patient deaths and, in turn, fulfills its regulatory obligations to report those deaths to the FDA.

As discussed in Section 3.2.2 below, there is a potential for doubling of the number of prescribers of mifepristone if the in-person dispensing requirement in ETASU C is removed from the Mifepristone REMS Program. Given the potential addition of new prescribers, in addition to the considerations described above, we conclude that we should maintain the requirement for prescriber certification, to ensure that providers meet the necessary qualifications and adhere to the guidelines for use. Our literature review supports that these requirements are still necessary, and the potential increase in new prescribers under the REMS is a further reason to maintain prescriber certification. Healthcare provider certification continues to be a necessary component of the REMS to ensure the benefits of mifepristone for medical abortion outweigh the risks. The burden of prescriber certification has been minimized to the extent possible by requiring prescribers to certify only one time for each applicant.

3.2.2. Evaluation of the requirement for the drug to be dispensed with evidence or other documentation of safe-use conditions (ETASU D)

In order to receive mifepristone for medical termination of pregnancy through 70 days gestation, the patient must sign a *Patient Agreement Form* indicating that the patient has received, read, and been provided a copy of the *Patient Agreement Form* and received counseling from the prescriber regarding the risk of serious complications associated with mifepristone for this indication. The *Patient Agreement Form* ensures that patients are informed of the risks of serious complications associated with mifepristone for this indication.

^e American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin Number 191, February 2018. Tubal Ectopic Pregnancy. <https://www.acog.org/clinical/clinical-guidance/practice-bulletin/articles/2018/03/tubal-ectopic-pregnancy>. Mifepristone is not effective for terminating ectopic pregnancy. Some of the expected symptoms experienced with a medical abortion (abdominal pain, uterine bleeding) may be similar to those of a ruptured ectopic pregnancy. A missed ectopic pregnancy that ruptures is a medical emergency that requires immediate surgical intervention.

In a number of approved REMS, *Patient Agreement Forms* or *Patient Enrollment Forms* ensure that patients are counseled about the risks of the product and/or informed of appropriate safe use conditions.^f

As a condition of certification under the Mifepristone REMS Program, healthcare providers must follow the guidelines for use of mifepristone, including reviewing the *Patient Agreement Form* with the patient, fully explaining the risks of the treatment regimen, and answering any questions the patient may have before receiving the medication. With this form, the patient acknowledges that they have received and read the form, and that they have received the counseling regarding when to take mifepristone, the risk of serious complications associated with mifepristone and what to do if they experience adverse events (e.g., fever, heavy bleeding). Both the healthcare provider and patient must sign the document and the patient must receive a copy of the signed form. In addition to the counseling described in the *Patient Agreement Form*, patients also receive a copy of the Medication Guide for mifepristone. Ultimately, the *Patient Agreement Form* serves as an important counseling component, and documentation that the safe use conditions of the Mifepristone REMS Program have been satisfied, as the prescriber is required to place the signed *Patient Agreement Form* in the patient's medical record.

Prior to the March 29, 2016 approval of the S-020 efficacy supplement for Mifeprex, FDA undertook a review of all elements of the REMS. At that time, the (b) (6), (b) (6), along with the (b) (6), (b) (6), recommended removal of the *Patient Agreement Form* (ETASU D). This recommendation received concurrence from the (b) (6) on February 23, 2016. The rationale for this recommendation in the 2016 (b) (6) review^g is summarized here as follows:

- The safety profile of Mifeprex is well-characterized over 15 years of experience, with known risks occurring rarely; the safety profile has not changed over the period of surveillance.
- Established clinical practice includes patient counseling and documentation of informed consent and evidence shows that practitioners are providing appropriate patient

^f REMS@FDA, <https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm>, Accessed November 15, 2021.

^g (b) (6) Clinical Review, NDA 020687/S20, dated March 29, 2016. <https://darrrts.fda.gov/darrrts/faces/ViewDocument?documentId=090140af803dc7bd&afrRedirect=386175573203745>

counseling and education; the *Patient Agreement Form* is duplicative of these established practices.

- Medical abortion with Mifeprex is provided by a small group of organizations and their associated providers. Their documents and guidelines are duplicated in the *Patient Agreement Form*.
- ETASUs A and C remain in place: The *Prescriber Agreement Form* and the requirement that Mifeprex be dispensed to patients only in certain healthcare settings, specifically, clinics, medical offices, and hospitals under the supervision of a certified prescriber, remain in place.

In light of a memorandum from the Director of the Center for Drug Evaluation and Research, an addendum to the (b) (6) March 29, 2016 review and a memorandum from the signatory authority in (b) (6) indicated that the *Patient Agreement Form* would be retained in the REMS.^{h,i}

The current review of literature from March 29, 2016 to July 26, 2021, is relevant to our assessment of the necessity of the *Patient Agreement Form* as part of the REMS. While our literature search yielded no publications which directly addressed this element of the REMS, we identified the following literature that focused on the informed consent process. These studies were reviewed for their potential relevance on this topic, though the articles do not directly assess the need for the *Patient Agreement Form* as a condition necessary to assure safe use of Mifepristone under ETASU D.

- Two studies^{1,2} (both authored by Dr. Grossman in 2021) used the *Patient Agreement Form* and additional clinic-specific written informed consent forms as part of the study methodology. One study evaluated medical abortion with pharmacist dispensing of mifepristone and another evaluated mail-order pharmacy dispensing. Safety and efficacy outcomes were not assessed regarding the element of consent in isolation or the *Patient Agreement Form*.
- Several studies included use of electronic or verbal consent. Two studies were conducted using signed electronic consent (Chong³, Kerestes⁴). Aiken⁵ reported that patients had the option of providing consent verbally and the discussion had to be recorded in the notes. Rocca⁶ described obtaining verbal informed consent from patients seeking medical abortion provided in pharmacies or government-certified

^h (b) (6) Review of proposed REMS modifications to Mifeprex. March 29, 2106.

ⁱ (b) (6) Summary of Regulatory Action for Mifeprex. March 29, 2016.

public health facilities by auxiliary nurse midwives (ANMs) in Nepal. Outcomes were not assessed regarding the single element of consent and its role in the efficacy of medical abortion.

- A retrospective chart review (Wiebe⁷) was conducted in Canada. This study included telemedicine abortions between January 31, 2017 and January 31, 2019 and a similar group of controls seen in the clinic during the same time frame, matched by date of initial appointment. As part of the telemedicine process, patients read a consent form (not specified whether they could view an electronic version) and gave verbal consent “witnessed by the counselor”. Again, outcomes were not assessed regarding the single element of consent and its role in the efficacy of medical abortion.

After review, we conclude that there are no outcome data from these studies that address the need for the *Patient Agreement Form* as a condition necessary to assure safe use of mifepristone. Nor do any of these studies provide evidence of whether the patient’s informed consent has been adequately documented under the process set out in the study protocol. Therefore, these studies do not provide evidence that would support removing ETASU D.

Although (b) (6) agrees that informed consent in medicine is an established practice, the National Abortion Federation’s 2020 Clinical Policy Guidelines for Abortion Care⁸ continue to include a detailed section on patient education, counseling, and informed consent. The guidelines state that these steps are essential parts of the abortion process; that they should be conducted by appropriate personnel, with accurate information, including about alternatives and potential risks and benefits; and that the patients must have an opportunity to have any questions answered to their satisfaction prior to any intervention. Under these guidelines, documentation must show that the patient affirms that they understand all the information provided and that the decision to undergo an abortion is voluntary. The guidelines specifically list the risks that must be addressed at a minimum, including those pertinent to medical abortion: hemorrhage, infection, continuing pregnancy, and death. Additionally, Practice Bulletins from ACOG⁹ and the Society of Family Planning also support detailed patient counseling.

In addition, trends in US clinical practice are developing which could negatively impact adequate patient counseling about the risks of medical abortion. One survey by Jones 2017¹⁰ of abortion providers in the United States and Canada prior to the COVID-19 pandemic did reveal strong adherence to evidence-based guidelines. However, this same survey noted continued increasing uptake of medical abortion by US providers. Grossman¹¹ conducted a US survey in

2019 which suggested that the number of obstetrician/gynecologists providing medical abortion care may be increasing and that uptake might increase if mifepristone were dispensed by pharmacies instead of being dispensed in-person. A subsequent survey of US obstetricians/gynecologists by Daniel in 2021¹² evaluated a subsample (n = 868) from a prior national survey of providers and found that 164 (19%) reported providing medical abortion in the previous year. Of those obstetrician/gynecologists not providing medical abortion, 171 (24%) said they would offer the method to their patients if the in-person dispensing requirement for mifepristone were removed. This indicates a potential doubling of providers (+ 104%, 95% confidence interval (CI): 97% –112%). There were geographical variations, with the largest potential increases being in the Midwest (+ 189%, 95% CI: 172% –207%) and the South (+ 118%, 95% CI: 103% –134%).

Based on the articles discussed above, removal of the in-person dispensing requirement from the Mifepristone REMS Program (as discussed below in section 3.2.3) could significantly increase the number of providers to a larger group of practitioners. The *Patient Agreement Form* is an important part of standardizing the medication information on the use of mifepristone that prescribers communicate to their patients, and also provides the information in a brief and understandable format for patients. The requirement to counsel the patient, to provide the patient with the *Patient Agreement Form*, and to have the healthcare provider and patient sign the *Patient Agreement Form*, ensures that each provider, including new providers, informs each patient of the appropriate use of mifepristone, risks associated with treatment, and what to do if the patient experiences symptoms that may require emergency care. The single-page *Patient Agreement Form* is in line with other elements of this REMS, in that it supports the requirement that certified prescribers be able to accurately assess a patient, counsel a patient appropriately and recognize and manage potential complications. The form is placed in the patient's medical record to document the patient's acknowledgment of receiving the information from the prescriber and a copy is provided to the patient. We determined, consistent with section 505-1(f)(2) of the FD&C Act, that this does not impose an unreasonable burden on providers or patients, and that the *Patient Agreement Form* remains necessary to assure the safe use of Mifepristone.

After considering potential burden on healthcare providers and patients and considering the available data discussed above, including the potential for increased prescribing of mifepristone if in-patient dispensing is removed from the REMS, we conclude that the *Patient Agreement Form* should remain a safe use condition in the REMS.

3.2.3. Evaluation of the requirement for drug to be dispensed only in certain healthcare settings (ETASU C)

Mifepristone applicants must ensure that mifepristone is available to be dispensed to patients only in clinics, medical offices, and hospitals by or under the supervision of a certified prescriber. This creates what we refer to in this document as an in-person dispensing requirement under the REMS; i.e., the patient must be present in person in the clinic, medical office or hospital when the drug is dispensed. The mifepristone REMS document states that mifepristone may not be distributed to or dispensed through retail pharmacies or settings other than these.

The following information contributed to our analysis of this requirement: Mifepristone REMS Program year-one assessment data, postmarketing safety information and literature review.

REMS Assessment Data

Reporting period for the Mifepristone REMS Program - April 11, 2019 through February 29, 2020

We evaluated information included in the one-year (1st)^j REMS assessment reports for the Mifepristone REMS Program, which included healthcare provider certification data, program utilization data, compliance data, audit results and patient exposure data.¹³ The assessment reports were submitted on April 10, 2020 by the NDA Applicant and April 15, 2020 by the ANDA Applicant and cover a reporting period from April 11, 2019 through February 29, 2020. During this reporting period, the NDA Applicant reported (b) (4) newly certified healthcare providers, and the ANDA Applicant reported (b) (4) newly certified healthcare providers in the Mifepristone REMS Program. The NDA Applicant reported a total of (b) (4) certified healthcare providers (includes new and previously certified) ordered mifepristone during the assessment reporting period, and the ANDA Applicant reported a total of (b) (4) certified healthcare providers ordered mifepristone during the assessment reporting period. The NDA Applicant estimated that a total of (b) (4) patients were exposed to mifepristone during the assessment reporting period. The ANDA Applicant reported an estimated total of (b) (4) patients were exposed to mifepristone during the reporting period.

During the reporting period, a small number of non-compliance events were reported. The authorized distributor for the NDA applicant reported to the NDA Applicant that they experienced deviations with scanning of the product serial numbers which were confirmed during the February 2020 audit. The authorized distributor conducted a root cause analysis and developed a corrective and preventive action (CAPA) on February 12, 2020. The CAPA was

^j This REMS assessment report was the first to be submitted following the approval of the single, shared system REMS for mifepristone.

validated and deployed with monitoring of the system through April 10, 2020. The corrective action will prevent similar events from occurring in the future.

January 27, 2020 through September 30, 2021

During the timeframe from January 27, 2020 through September 30, 2021, there were periods when the in-person dispensing requirement was not being enforced.

- On July 13, 2020, the United States District Court for the District of Maryland granted a preliminary injunction in the ACOG case to temporarily bar enforcement of the in-person dispensing requirement during the COVID-19 PHE.
- On January 12, 2021, the United States Supreme Court issued a stay of the injunction.
- On April 12, 2021, the FDA issued a General Advice Letter informing the applicants of the Agency's intent to exercise enforcement discretion during the COVID-19 public health emergency regarding the in-person dispensing requirement in the Mifepristone REMS Program.^{k,l}

To better understand whether there was any impact on safety or noncompliance during the periods when the in-person dispensing requirement was not being enforced, we requested additional information from the Applicants to provide for more comprehensive assessment of the REMS for the time period from January 27, 2020 (the effective date of the COVID-19 PHE) to September 30, 2021. We requested the Applicants provide a summary and analysis of any program deviation or noncompliance events from the REMS requirements and any adverse events that occurred during this time period that had not already been submitted to FDA. As part of an additional request for information for the REMS assessment report, the Applicants were also asked to submit the adverse events to FAERS and to notify FDA that the reports were submitted.

Between January 27, 2020 and September 30, 2021, the NDA Applicant distributed (b) (4) shipments representing (b) (4) tablets. The NDA Applicant reported that there were (b) (4) shipments representing a total of (b) (4) tablets sent to (b) (4) non-certified healthcare providers.^{m,n} (b) (4) of these healthcare providers subsequently became certified while (b) (4) did not. Of the (b) (4) healthcare providers who were not subsequently certified, (b) (4) returned a total of (b) (4)

^k FDA General Advice Letter for NDA 20687, April 12, 2021.

^l FDA General Advice Letter for ANDA 091178, April 12, 2021.

^m NDA 020687 September 9, 2021 response to the FDA's September 2, 2021 Information Request.

ⁿ NDA 020687 October 8, 2021 response to the FDA's June 30, 2021 Information Request.

Mifeprex tablets to the distributor. (b) (4) non-certified healthcare provider dispensed (b) (4) to a patient; no adverse events were reported. The NDA Applicant attributed the non-compliance observed to the authorized distributor's transition to a new platform. The NDA Applicant implemented a corrective and preventative action to address this issue, which we found to be acceptable.

The ANDA Applicant distributed (b) (4) shipments representing (b) (4) tablets of mifepristone from January 27, 2020 to September 30, 2021 and reported no instances of shipments to non-certified healthcare providers during this timeframe.

The NDA and the ANDA applicants reported a total of eight cases reporting adverse events between January 27, 2020 and September 30, 2021. These eight cases were also identified in the FAERS database and are described in the section below.

The number of adverse events reported to FDA during the COVID-19 PHE with mifepristone use for medical termination of pregnancy is small, and the data provide no indication that any program deviation or noncompliance with the Mifepristone REMS Program contributed to these reported adverse events. Further analysis of the adverse events is included below in the section on Pharmacovigilance Data.

Pharmacovigilance Data

The (b) (6) (b) (6) conducted a search of the FAERS database and the published medical literature to identify U.S. postmarketing adverse events that reportedly occurred from January 27, 2020 through September 30, 2021 with mifepristone use for medical termination of pregnancy.^{o,p}

The data for this time period were then further divided into date ranges when the in-person dispensing requirement was being enforced per the REMS (January 27, 2020 - July 12, 2020 & January 13, 2021 - April 12, 2021) versus when the in-person dispensing requirement was not being enforced (July 13, 2020 - January 12, 2021 (in-person dispensing requirement was temporarily enjoined) & April 13, 2021 - September 30, 2021 (in-person dispensing requirement was not being enforced because of the COVID-19 PHE)).

^c (b) (6). Pharmacovigilance Memorandum: Mifepristone and All Adverse Events. NDA 020687 and ANDA 091178. (b) (6) # 2007-525. Finalized April 12, 2021.

^p (u) (u) Pharmacovigilance Memorandum: Mifepristone and All Adverse Events. NDA 020687 and ANDA 091178. (b) (6) # 2007-525. Finalized December 16, 2021.

A total of eight cases that met the search criteria were identified in FAERS and no additional case reports were identified in the medical literature. Two of the eight cases reported adverse events that occurred when the in-person dispensing requirement in the REMS was being enforced (i.e., January 27, 2020 - July 12, 2020 & January 13, 2021 - April 12, 2021). These two cases reported the occurrence of uterine/vaginal bleeding (case 1) and uterine/vaginal bleeding and sepsis (case 2). Of note, uterine/vaginal bleeding and sepsis are labeled adverse events. Five of the eight cases reported adverse events that occurred when the in-person dispensing requirement was not being enforced (i.e., July 13, 2020 - January 12, 2021 & April 13, 2021 - September 30, 2021). These five cases reported the occurrence of ongoing pregnancy (case 3), drug intoxication and death approximately 5 months after ingestion of mifepristone (case 4), death [cause of death is currently unknown] (case 5), sepsis and death (case 6), and pulmonary embolism (case 7). Although these adverse events occurred during the period when the in-person dispensing requirement was not being enforced, the narratives provided in the FAERS reports for cases 5, 6, and 7 explicitly stated that mifepristone was dispensed in-person. Of note, ongoing pregnancy, and sepsis, including the possibility of fatal septic shock, are labeled adverse events. The remaining case from July 2021 reported the occurrence of oral pain/soreness (case 8) but did not provide sufficient information to determine the exact date of the adverse event. Based upon the U.S. postmarketing data reviewed, no new safety concerns were identified by (b) (6)

In addition to the FAERS data provided above, (b) (6) routinely monitors adverse events reported to FAERS and published in the medical literature for mifepristone for medical termination of pregnancy. (b) (6) has not identified any new safety concerns with the use of mifepristone for medical termination of pregnancy.

To enable additional review of adverse events, the Applicants were requested^q to provide a summary and analysis of adverse events reported with incomplete medical abortion requiring surgical intervention to complete abortion, blood transfusion following heavy bleeding or hemorrhage, ectopic pregnancies, sepsis, infection without sepsis, hospitalization related to medical abortion, and emergency department (ED)/urgent care encounter related to medical abortion. The Applicant for Mifeprex provided a summary of postmarketing safety information from March 29, 2016, when S-020 was approved, through September 30, 2021, on August 27 and October 8, 2021. During the time period in question, (b) (4) tablets were shipped, and

^q On August 5, 2021, an IR was sent to the Applicants requesting a summary and analysis of adverse events from March 29, 2016 through June 30, 2021 and from July 1, 2021 through September 30, 2021.

48 adverse events were received. The 48 adverse events included 4 deaths (one of which occurred in 2010 but was reported in 2017), 25 incomplete abortions requiring surgical intervention, 17 blood transfusions following heavy vaginal bleeding, 2 ectopic pregnancies, 7 infections (1 sepsis and 6 infection without sepsis), 13 hospitalizations, and 43 ED or urgent care visits related to medical abortion. For the period between January 27, 2020 and September 30, 2021, a time frame that includes the entire period when the COVID-19 public health emergency (PHE) has been in effect, there were three adverse events reported corresponding to the above cases from FAERS identified by (b) (6) case 1 (uterine/vaginal bleeding), case 2 (uterine/vaginal bleeding and sepsis), and case 4 (drug intoxication and death).

The ANDA Applicant provided a summary of postmarketing safety information from April 11, 2019 (date of ANDA approval) through September 30, 2021. On August 26, 2021, the Applicant provided distribution and adverse event information from April 11, 2019 through June 30, 2021. During this time period, a total of (b) (4) tablets were shipped. There were 7 adverse events including 3 deaths (1 from sepsis, 1 from bilateral pulmonary artery thromboemboli, 1 in a patient who complained of not being able to breathe), 1 ongoing pregnancy treated with uterine aspiration, 2 blood transfusions, 1 sepsis (with death), 1 hospitalization, and 3 ED or urgent care visits related to medical abortion. On October 12, 2021 the Applicant provided information from July 1, 2021 to September 30, 2021; there were no additional adverse events. For the period between January 27, 2020 and September 30, 2021, there were four adverse events reported corresponding to the above cases from FAERS identified by (b) (6) case 3 (ongoing pregnancy), case 5 (death unknown cause), case 6 (sepsis and death), and case 7 (pulmonary embolism).^r

The postmarketing data from FAERS were analyzed by (b) (6) to determine if there was a difference in adverse events between periods when the in-person dispensing requirement was being enforced and periods when the in-person dispensing requirement was not being enforced. Based on this review, we conclude that there does not appear to be a difference in adverse events between periods when the in-person dispensing requirement was being enforced and periods when the in-person dispensing requirement was not being enforced. This suggests that mifepristone may be safely used without an in-person dispensing requirement.

^r The eighth FAERS case, oral pain/soreness, was not within the scope of the August 5, 2021 IR and was not considered for this review of postmarketing safety information submitted by the Applicants in response to the IRs.

(b) (6) review of the Applicants' IR responses, which included the same cases identified by (b) (6) from FAERS, did not change our conclusion.^s

Literature Review

Published studies have described alternatives in location and method for dispensing mifepristone by a certified prescriber (or an equivalent healthcare provider in countries other than the US). Some studies have examined replacing in-person dispensing in certain health care settings with dispensing at retail pharmacies (Grossman², Wiebe⁷, Rocca⁶) and dispensing mifepristone from pharmacies by mail (Grossman¹, Upadhyay¹⁴, Hyland¹⁵). Other studies have evaluated two modes of dispensing by prescribers: (1) prescribers mailing the medications to women (Gynuity study [Raymond¹⁶, Chong³, Anger¹⁷], Kerestes⁴, Aiken⁵ (2021)) and (2) prescribers using couriered delivery of medications (Reynolds-Wright¹⁸). Other studies have evaluated dispensing mifepristone by mail by an entity described as "a partner organization" (Aiken¹⁹ (2017), Norton²⁰, Endler²¹). For ease of review, in the sections below that describe these studies, we have separated relevant references by the methodology used to dispense mifepristone.

Retail pharmacy dispensing

Three studies report medical abortion outcomes for retail pharmacy dispensing of mifepristone after clinical evaluation. Grossman² conducted a US-based study in which mifepristone and misoprostol were dispensed from a pharmacy partnered with the clinic where the participant had an evaluation by ultrasound and counseling. Of the 266 participants enrolled, 260 had known abortion outcomes. Complete abortion without additional procedure occurred in 243 participants (93.5% of those with known outcomes). Seventeen participants (6.5% of those with known outcomes) were diagnosed with incomplete abortion and underwent uterine aspiration. The reported proportion of complete abortion is within the range described in the approved mifepristone labeling. However, the finding represents a lower-than-expected efficacy based on the cohort's GA (84% of participants were at ≤ 56 days GA, a cohort for which the labeled success rate is 96.8%). No participants experienced a serious adverse event, were hospitalized, or required transfusion. Three participants had ED visits with treatment (intravenous hydration, pain medication, pelvic infection after uterine aspiration for incomplete abortion). The study's

^s The reporting period of (b) (6) assessment of the adverse events in FAERS is not identical to the time period for summaries of adverse events in the IRs to the Applicants. Therefore, the numbers of cases and adverse events summarized in (b) (6) assessment may differ from the numbers of cases and adverse events summarized by the Applicants in their responses to IRs (note that each case report may include more than one adverse event).

safety and efficacy outcomes are consistent with labeled frequencies. The majority of participants (65%) were very satisfied with the experience. There were some complaints from participants about not receiving all prescribed medications at the initial pharmacy visit, privacy not being adequately maintained, and perceived negative pharmacist attitude.

Overall, we conclude that this study has limited generalizability because it was conducted in two US states and involved partnered pharmacies, some of which were in the same building as the clinic. Additionally, all participating pharmacies in this study were required to have a pharmacist on duty during clinic hours who had been trained in the study protocol and was willing to dispense mifepristone. The study conditions may not be generalizable to US retail pharmacies; there is insufficient information to assess this. Rocca⁶ conducted an observational study evaluating 605 participants at ≤ 63 days GA who obtained medical abortions in Nepal by comparing the provision of medical abortion service by newly trained nurse midwives in pharmacies to medical abortion provided in government-certified clinics. Participants who presented to pharmacy study sites underwent clinical screening including a pelvic exam by trained nurse midwives at the pharmacy (which was equipped with an examination room) and if eligible for medical abortion, were dispensed mifepristone and misoprostol in the pharmacy at the time of their visit. Participants who presented to public health facilities underwent clinical screening including pelvic examination by abortion providers including trained nurse midwives and if eligible for medical abortion were dispensed mifepristone and misoprostol in the clinic at the time of their visit. The authors reported that, with respect to complete abortion ($>97\%$) and complications (no hospitalizations or transfusions), evaluation and dispensing in pharmacy was non-inferior to in-clinic evaluation and dispensing.

Wiebe,⁷ in a retrospective, chart review study conducted in Canada, compared abortion outcomes of 182 women at ≤ 70 days GA who underwent medical abortion with telemedicine consult, and either received medications by courier or picked them up at a local pharmacy, with outcomes of a matched control cohort of 199 women who received the medications at a pharmacy after an in-clinic visit. The groups had similar documented complete medical abortion outcomes (90%, calculated maintaining subjects with unknown outcomes in the denominator; $\geq 95\%$ calculated with known outcomes only). The telemedicine group had one case of hemorrhage (0.5%) and one case of infection requiring antibiotics (0.5%) compared with no cases of hemorrhage or infection requiring antibiotics in the in-clinic cohort. The telemedicine group had more ED visits (3.3% compared to 1.5% in-clinic cohort). Both models of dispensing mifepristone resulted in efficacy and safety outcomes within labeled frequency.

None of the three studies described above allow a determination regarding differences in safety between in-person dispensing by a certified prescriber in a health care setting and dispensing through a retail pharmacy, due to limitations on the generalizability of the studies to the current retail pharmacy environment in the US. The outcome findings from the one US study (Grossman²), in which the pharmacies were partnered with prescribers, may not be generalizable to much of the US as they do not reflect typical prescription medication availability with use of retail pharmacy dispensing. Although retail pharmacy dispensing of mifepristone and misoprostol in Canada has been described in the literature, there are important differences in healthcare systems between Canada and the US that render the findings from studies in Canada (Wiebe⁷) not generalizable to the US. In the Wiebe study, timely provision of medication from the retail pharmacy was accomplished by either courier to the woman or faxed prescription to the woman's pharmacy. It is unknown whether conditions that allow timely access to medications for medical abortion would occur in retail pharmacies throughout the US. Canada's federal government has reaffirmed that abortion is an essential health service^t which may have implications affecting access to medical abortion from retail pharmacies in Canada. The Rocca⁶ study evaluated medical abortion provided in Nepali pharmacies and essentially moved the abortion provider and clinical examination into the pharmacy, a scenario that is not, at this time, applicable to the US retail setting.

Mail order pharmacy

Grossman¹ published an interim analysis of an ongoing prospective cohort study evaluating medical abortion with mifepristone and misoprostol dispensed by mail-order pharmacy after in-person clinical assessment. All participants were evaluated for eligibility during a clinic visit with GA up to 63 days confirmed with either an ultrasound or examination; instead of receiving medication at the clinic visit, participants received medications from a mail-order pharmacy. A total of 240 participants have been enrolled; three participants did not take either medication. A total of 227 (94.6%) provided some outcome information, of whom 224 provided abortion outcome information. Complete abortion without additional procedures occurred in 217 participants (96.9% of those with known outcomes). Two (0.9%) participants experienced serious adverse events (SAE); one received a blood transfusion, and one was hospitalized overnight. Nine (4%) participants attended 10 ED visits. In this interim analysis, the outcomes are consistent with labeled frequencies. With respect to the time interval between a

^t As noted in Mark²³ and Martin²⁴, most provincial and federal health insurance programs in Canada cover medical abortion, and covered services are free at the point of care.

participant's clinic visit and receipt of medications, of the 224 participants with known abortion outcomes, 184 (82.1%) received medication within 3 days. However, 17% received between 4-7 days and one participant waited over 7 days for receipt. Seven of 216 (3.2%) participants who completed the day-3 survey reported compromised confidentiality (e.g., someone found their medication, privacy concerns).

Upadhyay¹⁴ reports findings from a retrospective cohort study of 141 women undergoing medical abortion in the US without a consultation or visit. Eligibility was assessed based on a participant-completed online form collecting pregnancy and medical history. Participants who were considered eligible received medication delivered by a mail-order pharmacy. Three interactions via text, messaging or telephone occurred to confirm medication administration, assessment of expulsion and pregnancy symptoms, and results of a 4-week home pregnancy test. Abortion outcome was determined by either the day 3 assessment or the 4-week pregnancy test. The investigators reported a complete abortion rate without additional procedures of 95% (105 participants out of 110 for whom outcomes were known) and stated that no participants had any major adverse events. The proportion of abortion outcomes assessed at 3 days versus 4 weeks is not reported. Regardless, determining outcomes at 3 days is insufficient to determine outcome rates or safety findings because a 3-day follow-up period is too short. Additionally, a substantial number of participants (31) provided no outcomes information. Among the 141 participants enrolled, 128 had any follow-up contact with the study staff, and 110 provided outcomes information. Excluding outcomes of 22% of the cohort is a limitation of this study. This study used a model with numerous deviations from standard provision of medical abortion in the US, such as no synchronous interaction with the prescriber during informed consent or prior to prescribing medication, no confirmation of self-reported medical, surgical, and menstrual history. Further, follow-up information based on a 3-day period is insufficient to determine outcome rates or safety findings. These deviations, limited follow-up information, and small sample size limit the usefulness of this study.

Hyland¹⁵ describes findings from a cohort study in Australia evaluating medical abortion outcomes utilizing telemedicine and a central mail order pharmacy. All participants obtained screening tests including ultrasound confirmation of GA. A total of 1010 participants completed the screening process and were provided mifepristone and misoprostol. Abortion outcomes were determined for 754 (75%) of the 1010. Outcomes for the remaining 256 participants (25%) were not included because 31 provided no relevant information after shipment, 14 reported not taking misoprostol, and 211 did not have "full follow up" (i.e., known outcome of either complete medical abortion, uterine evacuation, or ongoing pregnancy with plan to continue).

Complete abortions without additional procedures occurred in 727 participants (96% of those with definitively documented outcomes) and is consistent with labeled efficacy. Of the 754 participants included in the analysis 717 (95%) had no face-to-face clinical encounters after medications were mailed while 21 (3%) were admitted to the hospital and 16 (2%) had an outpatient encounter. One participant who was hospitalized and underwent a surgical uterine evacuation received a transfusion. Not included in the findings are 7 hospitalizations occurring in 7 participants who did not have “full follow up”. The authors do not report any other adverse events and conclude use of the telemedicine medical abortion service is safe. The reasons for hospitalization are not discussed by the authors; therefore, it is unknown why the patients were hospitalized. Although the reported number of hospitalizations (3%) is higher than the less than 1% in the FDA-approved mifepristone labeling, conclusions regarding the safety findings in this study cannot be made in the absence of information about the reasons for hospitalization. Other limitations of this study include incomplete information about outcomes with face-to-face encounters, and not reporting outcomes of 25% of the enrolled cohort.

Overall, the three studies evaluating mail order pharmacy dispensing suggest that the efficacy of medical abortion is maintained with mail order pharmacy dispensing. In the Grossman¹ study, the interim analysis, although small, does not raise serious safety concerns. We note that 18% of participants did not receive medications within 3 days; the potential for delay in receiving medication by mail could limit the GA eligible for medical abortion through mail order pharmacy dispensing, because women at GA closer to 70 days might not receive medication in time. A small proportion (3%) of participants raised concerns regarding the issues of confidentiality and privacy. Safety findings from the Hyland¹⁵ study are difficult to interpret. Although only one transfusion is reported, and the authors state the findings demonstrate safety, the higher hospitalization rates, and lack of information on the reasons for hospitalization do not allow any conclusions about safety findings. Lastly, the Upadhyay¹⁴ study had no reported adverse events, but the findings are less useful because of the limited follow-up, and because medical abortions were provided using a model with numerous deviations from standard provision of medical abortion in the US.

Clinic dispensing by mail

A total of five studies evaluated clinic dispensing by mail.^{3,4,5,16, 17} Gynuity Health Projects conducted a prospective cohort study (the “TelAbortion” study) evaluating use of telemedicine for remote visits and mifepristone being dispensed from clinics via overnight or regular tracked mail. Three publications reviewed have reported outcomes for the Gynuity population

exclusively: Raymond¹⁶ from May 2016 to December 2018, Chong³ from May 2016 to September 2020 and Anger¹⁷ from March 2020 to September 2020. Due to the pandemic, the Gynuity study deviated from the protocol requirement of confirmation of GA by examination or ultrasound for many participants treated from March 2020 onward (although none of the three publications reported on the single element of dispensing mifepristone from the healthcare setting by mail). A fourth study, Kerestes,⁴ reports outcomes of medical abortion at the University of Hawai'i from April 2020 to November 2020: seventy-five (of whom 71 were enrolled in the Gynuity study) of the 334 participants in Kerestes were dispensed mifepristone by mail after a telemedicine consult. The section below discusses these four studies from the US as well as a large UK study by Aiken⁵ (2021).

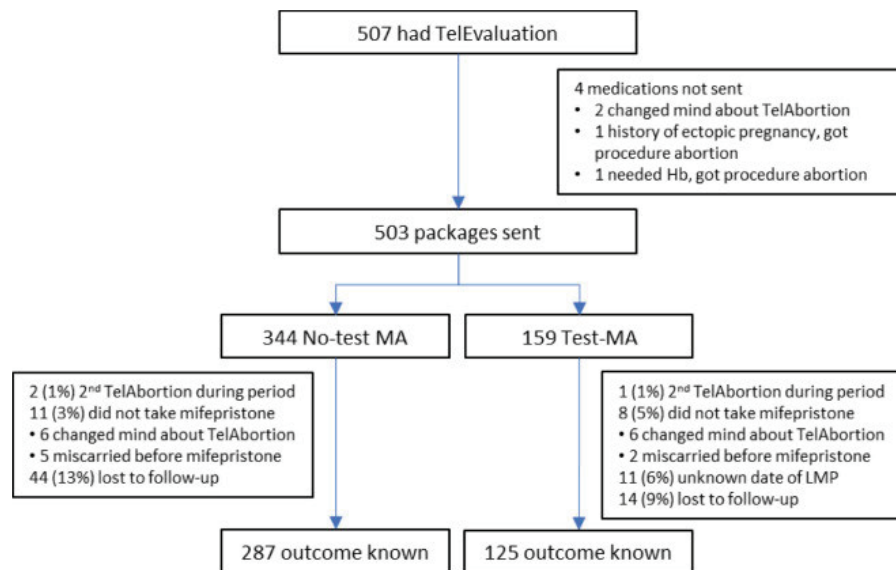
Raymond¹⁶ (2019) reported outcomes from the Gynuity study prior to the pandemic. In the TelAbortion study, participants were not required to have an in-person clinic visit; rather, they obtained screening tests at laboratories and radiology offices and then communicated with the abortion provider by videoconference. If the participant was eligible for treatment, the provider dispensed the medications by mail. Of 433 women screened, 165 (38%) either declined to schedule the videoconference or did not keep the videoconference appointment. Among the 268 participants evaluated via videoconference, medication packages were sent to 248. Abortion outcomes were determined for 190 (77%) of the 248; outcomes for 58 (23%) participants were unknown. Complete abortion without additional procedures occurred in 177 participants (93% of those with known outcomes). The investigators obtained follow-up information from 217 participants after package shipment; there were two hospitalizations (one received a transfusion for severe anemia despite having had a complete abortion), and 16 other participants (7%) had clinical encounters in ED and urgent care centers. The reported outcomes in Raymond¹⁶ (2019) are similar to outcomes described in approved labeling except the combined ED/urgent care center encounters (7%) exceeded the ED visits in approved labeling (2.9-4.6%). The authors note that half of the ED/urgent care visits did not entail any medical treatment and opine that the increased number of visits may have been due to the study participants living farther from the abortion providers.¹⁶ All participants received medications within 8 days.

Chong³ updated the findings from the Gynuity study described in Raymond¹⁶ and reported on 1157 medical abortion outcomes, of which approximately 50% occurred during the period of the COVID-19 PHE. Although a screening ultrasound was required per the protocol, sites determined in 52% (346/669) of abortions that occurred during the period of the COVID-19 PHE that, in order to avoid potential exposure to COVID-19 at a health care facility, those

participants were not required to obtain a screening ultrasound. Use of urine pregnancy test to confirm abortion completion also increased from 67% (144/214) in the 6 months prior to the pandemic to 90% (602/669) in the 6 months during the pandemic. Of the 1390 participants to whom medicine packages (containing both mifepristone and misoprostol) were mailed, 1157 (83.2%) had known abortion outcomes. Complete abortion without a procedure occurred in 1103 participants (95% of the those with a known outcome). Ten women experienced an SAE (5 transfusions (0.4%) and 7 hospitalizations (0.7%)) and 70 (6%) participants had unplanned clinical encounters in ED/urgent care. Surgical interventions were required in 47 participants (4.1% of 1390) to complete abortion. The reported outcomes in this study are similar to outcomes described in approved labeling, except that the combined ED/urgent care center encounters (6%) exceeded the ED visits in approved labeling (2.9-4.6%).

Anger¹⁷ compared outcomes among participants enrolled in the Gynuity study who did versus did not have confirmation of GA/intrauterine location with an examination or ultrasound from 10 jurisdictions across the US. These participants were screened for enrollment from March 25 through September 15, 2020. All participants had a telemedicine consultation and received mifepristone and misoprostol by mail from the healthcare facility. Determination of which participants did not require confirmation of GA by examination or ultrasound to be eligible depended on the study clinician's assessment of eligibility for "no-test medication abortion"^u based on a sample protocol published by Raymond²² (2020). There were two key differences between the two groups. Participants for whom the study clinician determined a pre-abortion ultrasound was required were more likely than the participants who had no ultrasound or examination to live further than 150 miles from the clinic (51.2% vs. 31.7%) and were more likely to have a GA above 63 days (12.0% vs. 1.7%). The study sites shipped 503 medication packages during the analysis period; 344 packages went to the "no test" group while 159 went to the "test" medical abortion cohort (see figure below). However, because the two cohorts were not randomized in this study, they had different baseline characteristics. Consequently, findings based on the comparisons between the two cohorts should be interpreted carefully.

^u "No-test medication abortion" refers to medical abortion provided without a pretreatment ultrasound, pelvic examination, or laboratory tests when, in the judgment of the provider, doing so is medically appropriate (appropriateness based on history and symptoms); "no-test medication abortion" does include post-abortion follow up. A sample protocol is described by Raymond et al.²²



Source: Figure 1 in this publication. MA= medical abortion.

The investigators' analyses excluded 91 (18% of 503; 57 in the no-test group and 34 in the test group) participants because they did not provide a date of the last menstrual period (LMP), did not take mifepristone, or did not have a recorded abortion outcome. Overall, 410 participants (81.5% of 503) provided outcomes data. There were no reported ectopic pregnancies in either group. The number of ED/urgent care visits and the proportion of unplanned clinical encounters that led to medical treatment were not reported. In the no-test group, complete medical abortion was confirmed in 271 participants who took medications (94% among those with known outcome). In the no-test cohort, two participants were "hospitalized and/or blood transfusion," and 36 (12.5%) had an unplanned clinical encounter (participant sought in-person medical care related to abortion and the visit was not planned prior to abortion).

In the test medical abortion group, complete abortion was confirmed in 123 participants (of 125 with known outcomes); the completion rate was 98% among those with known outcomes. In the test medical abortion group, one participant was "hospitalized and/or blood transfusion," and 10 (8.0%) had an unplanned clinical encounter. The authors concluded that, compared to participants who had an ultrasound prior to medical abortion, those without an examination prior to medical abortion were more likely to require procedural interventions and had more unplanned clinical encounters.

Kerestes⁴ was the only publication that linked outcomes of medical abortion with different delivery models. Participants included in the report had GA up to 77 days and received

medications in Hawaii between April 2020 and January 2020. A total of 334 medication packages (to 330 unique participants) were dispensed containing mifepristone and misoprostol; three different delivery models were used concurrently: 110 (32.9%) had traditional in-person visits, 149 (44.6%) had telemedicine consultation with in-person pick-up of medications, and 75 (22.5%) were sent medications by mail (71 of these were enrolled through Gynuity's TelAbortion study). Seven participants of the 330 participants who received 334 medication packages reported that they did not take them and were excluded from analysis of the outcomes. Among participants with follow-up data, the rates of successful medical abortion without surgery were 93.6%, 96.8%, and 97.1% in the in-clinic group, telemedicine + in-person pickup group, and telemedicine + mail group, respectively; these were consistent with outcomes in approved labeling. Blood transfusion was given to two participants (both in the telemedicine + in-person pickup group). Eleven participants went to an ED. Although ED visits occurred the most frequently in the telemedicine + mail group (four participants or 5.8%) and the least in the in-person group (two participants or 2.1%), the study reported no increases in other serious adverse events.

Taken together, the three Gynuity study reports^{3,16,17} and Kerestes⁴ support dispensing mifepristone and misoprostol by mail after a telemedicine visit. Efficacy was maintained in all four studies. All of the studies reported SAEs frequencies comparable to labeled rates, except two of the Gynuity study reports (Raymond¹⁶, Chong³) and Kerestes⁴ report a higher frequency of ED/urgent care visits than the labeled frequency of ED visits. We do not know whether the reporting of combined ED and urgent care visits represents an increased rate of ED visits compared to the labeled rate of ED visits (2.9-4.6%). Other labeled SAEs (e.g., transfusion) occur infrequently (< 1%).

Aiken⁵ (2021) reports outcomes of medical abortion up to 70 days GA in the UK before and during the pandemic in a retrospective cohort study. In the UK, prior to the COVID-19 pandemic, all patients attended an in-clinic visit where they received an ultrasound, were administered mifepristone in the clinic, and given misoprostol in-clinic for use at home (traditional model). During the pandemic, medical abortion consultations were performed remotely by telephone or video. Based on the consultation and questionnaire (including date of last menstrual period; menstrual, contraceptive and medical history; symptoms; risk for ectopic pregnancy), an assessment of eligibility for treatment via telemedicine was made. If eligible, medications were delivered to participants via mail or were made available for collection from the clinic for use at home. If the participant was assessed to be ineligible for treatment via

telemedicine, an in-person assessment with ultrasound was performed and medications were provided from the clinic for home use (hybrid model).

The study compared the two cohorts: 22,158 obtained medical abortion before the pandemic and had in-person visits and dispensing (traditional model) and 29,984 obtained medical abortion during the pandemic with either in-person visit and in-person dispensing, or a telemedicine visit and dispensing by mail or picked up from the clinic (hybrid model). Outcomes were obtained from electronic records and incident databases. Outcomes of all hospitalizations related to abortion, ED visits, infection without sepsis, and hemorrhage without transfusion were not reported. The investigators' analysis for non-inferiority determined the efficacy and safety were comparable between both cohorts. Complete abortion occurred in > 98% in both cohorts. Hemorrhage requiring transfusion was reported in 0.04% and 0.02% of the traditional and hybrid cohorts, respectively; this is lower than the labeled 0.5% transfusion rate. There were no severe infections requiring hospitalization, major surgery or deaths reported.

A secondary analysis of the hybrid cohort was reported. Within the 29,984-person hybrid model cohort, 11,549 (39%) abortions were conducted in-person (in-person assessment with ultrasound was performed and medications provided from the clinic for home use) and 18,435 (61%) abortions were provided by telemedicine visit, without tests or confirmation of GA/intrauterine position by ultrasound, and medications either mailed or picked up from the clinic. Outcomes stratified by type of mifepristone dispensing were not reported. The rate of complete abortion was slightly higher in the telemedicine group (99.2%) than that in the in-person group (98.1%). There were no significant differences in the rates of reported SAEs. Adjustments for clinical and demographic characteristics were made because the two groups differed in baseline characteristics, including a higher proportion of pregnancies with GA over 6 weeks in the in-person group (68.2% compared with 55.1%). The authors conclude a hybrid model for medical abortion that includes no-test medical abortion^u (no ultrasound, no pelvic exam, no pregnancy test) is effective and safe.

We conclude that although the Aiken⁵ (2021) study has a large sample size and includes 85% of all medical abortions performed in England and Wales during the study period, the study has limitations. The authors acknowledge the main limitation of their study was that analysis was based on deidentified information in the NHS database and the investigators were unable to verify the outcomes extracted. Other limitations included that their search only captured

outcomes in electronic records and incident databases that met the authors' defined threshold for SAE reporting, and that the labeled abortion outcomes considered serious, such as hospitalizations related to abortion, infection without sepsis, hemorrhage without transfusion, or ED/urgent care visits, were not all included in the authors' definition of serious adverse event.

Data from the mail order dispensing studies with telemedicine visits from Gynuity (Raymond, Chong and Anger),^{3,16,17} Kerestes⁴, and Aiken⁵ (2021) support that efficacy of medical abortion was maintained. The Aiken⁵ study appears to be of sufficient sample size to determine whether safety outcomes with mail dispensing differ from in-person dispensing; however, the study's design did not capture all serious safety outcomes, thus limiting the certainty of the findings. Study reports of Raymond¹⁶ Chong³, and Kerestes⁴ all suggest there may be an increase in ED/urgent care visits with telemedicine visits and dispensing by mail without increases in other adverse events. Anger's¹⁷ comparative analysis suggests a pre-abortion examination may decrease the occurrence of procedural intervention and decrease the number of unplanned visits for postabortion care. Overall, despite the limitations noted, these studies support that dispensing by mail is safe and effective. Although the literature suggests there may be more frequent ED/urgent care visits related to the use of mifepristone when dispensed by mail from the clinic, there are no apparent increases in other SAEs related to mifepristone use. One reason for the increase in frequent ED/urgent care visits in the Raymond¹⁶ publication, according to its authors, may have been that a substantial proportion of participants lived significant distances from their providers and increased distances have been associated with higher use of ED following treatment. Raymond¹⁶ reported that half of the participants who had an ED/urgent care visit did not require medical treatment.

Clinic dispensing by courier

Reynolds-Wright¹⁸ reported findings from a prospective cohort study of 663 women at less than 12 weeks' GA in Scotland undergoing medical abortion at home with use of telemedicine during the pandemic (from April 1 to July 9, 2020). The majority of medical abortions (78.7%) used telemedicine visits, eliminated pre-abortion ultrasound, and provided mifepristone for pick up at the service or by couriered delivery to woman's home. The number of couriered deliveries was not reported; thus, this study does not provide abortion outcomes separately for couriered delivery of mifepristone and misoprostol. With access to NHS regional hospital databases, the investigators were able to verify pregnancy outcomes and complications. Of the 663 participants, 642 (98.2%) were under 10 weeks GA, 21 (1.8%) were between 10 and 12 weeks

GA, and one participant was never pregnant. A total of 650 participants had complete abortion without requiring surgical intervention (98%), 5 (0.8%) an ongoing pregnancy and 4 (0.6%) an incomplete abortion. The outcomes from this study in Scotland are consistent with labeled mifepristone outcomes. The study shares the same limitations as the Aiken⁵ (2021) study.

Partner organization dispensing by mail

Women on Web (WoW), an internet group, connects patients and providers outside of the US and provides medical abortion globally, dispensing mifepristone through “a partner organization” by mail.^v Medical abortion eligibility is determined using an online questionnaire with asynchronous physician review. If eligible, medications are mailed to the women. WoW provides help and support by email or instant messaging.

Aiken¹⁹ (2017) conducted a population-based study analyzing findings from 1,636 women in the Republic of Ireland and Northern Ireland who were sent medications between 2010 and 2012. Receipt of medications was confirmed for 1,181 women, among whom 1,023 confirmed use of mifepristone and misoprostol; outcome information was available for 1,000 (61% of women sent medications). Of the 1,000 women, the majority (781, 78%) were less than 7 weeks GA and 219 (22%) were at 7-9 weeks. Complete abortion without surgical intervention occurred in 947 (94.7% of 1,000 with known outcome); 7 (0.7%) women received a blood transfusion, 26 (2.6%) received antibiotics (route of administration undetermined) and 87 (8.7%) sought medical care at a hospital or clinic for symptoms related to medical abortion. Hospitalizations related to abortion were not reported. The reported proportion of complete abortion is within the range labeled for medical abortion up to 70 days (92.7-98.1%). However, the finding of 94.7% complete abortion represents a lower-than-expected efficacy based on the cohort’s GA (almost 80% less than 7 weeks, labeled success for medical abortion \leq 49 days is 98.1%). This study has limitations, including outcomes based on self-report without validation of completed abortion by examination or laboratory testing, and no known outcomes for 39% of study cohort. Additionally, the authors noted medical abortion was provided in a legally-restrictive setting, where the law provided a maximum penalty of life imprisonment for the woman undergoing the abortion, which may affect participants’ self-reporting.

^v In March 2019, FDA sent a WL to Aidaccess.org, a group affiliated with WoW. Aidaccess.org received this WL because it was introducing misbranded and unapproved new drugs into the U.S. In the context of this REMS review, studies involving WoW are included solely for purposes of evaluating of data regarding the methods of dispensing mifepristone.

Endler²¹ and Norten²⁰ have reported outcomes from WoW cohorts but do not provide relevant information on mifepristone dispensing by mail, because neither provide meaningful outcomes data for consideration. Endler²¹ compared the outcomes of self-reported heavy bleeding and clinical visits occurring during the “first or second day of abortion” that occurred in women undergoing medical abortion at 9 weeks GA or less, with outcomes from women at more than 9 weeks GA. Outcome data from day 1 or 2 is of limited usefulness. Norten²⁰ describes findings from a survey of women who were sent medical abortion medication through WoW and provided self-reported outcomes. Results were based on surveys returned from only 37% of participants, a return rate that is too low for the study to be considered valid.

WoW uses a model with numerous deviations from the standard provision of medical abortion in the US. For example, this model has no synchronous interaction with the prescriber during informed consent or prior to prescribing medication and no confirmation of self-reported medical, surgical, and menstrual history or confirmed pregnancy testing. Further, although Aiken¹⁹ (2017) is a large cohort study, the outcomes are self-reported with no verification of complete abortion by laboratory or clinical evaluation and 39% of outcomes are unaccounted for. These limitations in the Aiken study result in the data being insufficient to determine the safety of dispensing mifepristone by mail through a partner organization.

4. Discussion

After review of the published literature, safety information collected during the COVID-19 PHE, postmarketing data, information from the first Mifepristone REMS Program assessment report, responses to information requests to the Applicants, and information provided by advocacy groups, individuals and the plaintiffs in the *Chelius v. Becerra* litigation, we conclude that the REMS can be modified to reduce burden without compromising patient safety.

Prescriber Certification

None of the publications we reviewed would support a conclusion that a healthcare provider who prescribes mifepristone does not need to meet the qualifications included in the Mifepristone REMS Program as described above in section 3.2.1. Absent these provider qualifications, serious complications associated with medical abortion, including missed ectopic pregnancy and heavy bleeding from incomplete abortion, would not be detected or appropriately managed.

We conclude that prescriber certification (ETASU A) should be maintained. The current process requires the prescriber to agree to the requirements of the Mifepristone REMS Program and to attest that they meet the qualifications described in section 3.2.1 above. The REMS has been structured to minimize burden to prescribers by requiring only a one-time certification by the prescriber for each Applicant. We have determined that healthcare provider certification continues to be necessary to ensure the benefits outweigh the risks, especially considering that, if the in-person dispensing requirement is removed from the Mifepristone REMS Program, the number of new providers may increase (see discussion in section 3.2.2 above).

Drug to be dispensed with evidence or other documentation of safe use conditions

The requirement to counsel the patient and provide them with the *Patient Agreement Form* ensures that each patient is informed of the appropriate use of mifepristone, the risks associated with treatment, and what to do if they experience symptoms that may require emergency care.

In 2016, we initially recommended eliminating the *Patient Agreement Form* (see section 3.2.2), though the form was ultimately maintained as part of the REMS. As discussed above, our current literature review has indicated that there is no basis to remove the *Patient Agreement Form* from the REMS. In addition, surveys we reviewed suggest that if the in-person dispensing requirement for mifepristone is removed, there could be a potential doubling of medical abortion providers. This potential doubling of medical abortion providers supports the continued need to ensure that patients are consistently provided patient education under the Mifepristone REMS Program regarding the use and risks of mifepristone. The *Patient Agreement Form* is an important part of standardizing the medication information that prescribers communicate to their patients, including new prescribers, and also provides the information in a brief and understandable format to patients. We determined, in accordance with section 505-1(f)(2) of the FD&C Act, that this does not impose an unreasonable burden on providers or patients.^w

Given the likelihood of a potential increase in new prescribers if the in-person dispensing requirement is removed from the Mifepristone REMS Program, we conclude that maintaining the *Patient Agreement Form* remains necessary to assure safe use at this time.

^w The *Patient Agreement Form* can be signed in person or through other means.

Drug to be dispensed only in certain healthcare settings

As discussed above in section 3.2.3, our evaluation of information submitted by the applicants in the one-year (1st) REMS assessment report for the Mifepristone REMS Program and in response to follow-up requests from the Agency indicates that the number of adverse events reported to FDA during the COVID-19 PHE with mifepristone use is small, and the data provide no indication that any program deviation or noncompliance with the Mifepristone REMS Program contributed to these adverse events. We further conclude, based our review of the postmarketing safety data from FAERS during the COVID-19 PHE and information submitted by the applicants for the timeframe of January 27, 2020 through September 30, 2021, that there does not appear to be a difference in adverse events between periods during the COVID-19 PHE when the in-person dispensing requirement was being enforced and periods when the in-person dispensing requirement was not being enforced; nor have we identified any new safety concerns with the use of mifepristone for medical termination of early pregnancy.

Alternatives to in-person dispensing of mifepristone have been investigated in several studies and countries. The literature review identified 15 publications^x that assessed safety outcomes from various medication delivery models (US, UK, Canada, Ireland, Australia, Nepal), including dispensing by retail and mail order pharmacies, prescribers mailing medications or using couriered service to deliver medications, and dispensing by “partner organizations”. The ability to generalize the results of these studies to the US population is hampered by differences in pre-abortion care (e.g., telemedicine versus in-person, testing), and the usefulness of the studies is limited in some instances by small sample sizes and lack of follow-up information on outcomes with regard to both safety and efficacy.

In addition, there are factors which complicate the analysis of the dispensing element alone. Some of these factors are: (1) only a few studies have evaluated alternatives for in-person dispensing of mifepristone in isolation; for example, most studies on mail dispensing of mifepristone also include telemedicine consultation, and (2) because most SAEs with medical abortion are infrequent, though they can be life threatening, further evaluation of changes in dispensing would require studies with larger numbers of participants. We did not find any large clinical studies that were designed to collect safety outcomes in healthcare systems similar to the US.

^x The 15 publications correspond to endnote numbers: 1-7, 14-21.

Based on the literature identified by our review, dispensing mifepristone by mail from the clinic or from a mail order pharmacy does not appear to jeopardize the efficacy of medical abortion. The studies we reviewed are not adequate on their own to establish the safety of the model of dispensing mifepristone by mail, although the safety and efficacy outcomes reported in these studies remain within the ranges described in mifepristone labeling except for increased numbers of ED/urgent care visits and hospitalizations.

Four publications (Raymond¹⁶, Chong³, Anger¹⁷ and Kerestes⁴), describe a relevant US cohort where dispensing mifepristone from the clinic by mail was paired with telemedicine visits. These studies showed that efficacy was maintained and there was no increased frequency of SAEs except for higher ED/urgent care visits. The increased ED/urgent care visits were not associated with increases of other SAEs, and in the view of one study's authors (Raymond¹⁶), may be associated with participants being located significant distances from their providers. The Aiken⁵ (2021) study of a large UK cohort where the clinics mailed mifepristone report small (lower than labeled) occurrences of transfusion and no significant infections requiring hospitalization. In Grossman¹ and Hyland¹⁵, where the pharmacies mailed mifepristone after prescribers confirmed GA, efficacy is maintained. Grossman's¹ interim analysis found no increases in SAEs. Hyland¹⁵ reported higher numbers of hospitalizations but did not report increases of other SAEs. Overall, while the studies assessing mifepristone dispensing by mail suggest more frequent encounters with healthcare providers, they generally support a conclusion that dispensing by mail is safe. Despite the limitations of the studies we reviewed, we conclude that overall, the outcomes of these studies are not inconsistent with our conclusion that, based on the 1st year REMS assessment report and postmarketing safety data, mifepristone will remain safe, and efficacy will be maintained if the in-person dispensing requirement is removed from the Mifepristone REMS Program.

Based on the REMS assessment data, FAERS data from the time period when the in-person dispensing requirement was not being enforced, our review of the literature, and information provided by advocacy groups, individuals, the Applicants, and the plaintiffs in the *Chelius v. Becerra* litigation, we conclude that mifepristone will remain safe and effective for medical abortion if the in-person dispensing requirement is removed, provided all the other requirements of the REMS are met, and pharmacy certification is added as described below.

Removing the in-person dispensing requirement will render the REMS less burdensome to healthcare providers and patients and provided all other requirements of the REMS are met, including the additional requirement for pharmacy certification, the REMS will continue to

ensure that the benefits of mifepristone for medical abortion outweigh the risks. Therefore, to reduce the burden imposed by the REMS, the Mifepristone REMS Program should be modified to remove the in-person dispensing requirement, which would allow, for example, dispensing of mifepristone by mail via certified prescribers or pharmacies, in addition to in-person dispensing in clinics, medical offices and hospitals as currently outlined in ETASU C.

New requirement to be added for pharmacy certification

The current distribution model requires the certified prescriber to dispense mifepristone directly to the patient in a clinic, medical office, or hospital. During the periods when the in-person dispensing requirement was not being enforced, both applicants used mail order pharmacies to receive and hold mifepristone on behalf of the certified healthcare providers who had purchased the product.^{j,y,z} Pursuant to a prescription for mifepristone, the mail order pharmacy would ship the product to a named patient.

The Mifepristone REMS Program continues to require that mifepristone be prescribed only by certified prescribers. With the removal of the in-person dispensing requirement, however, the drug is no longer required to be dispensed only in a clinic, medical office or hospital. Under the REMS as modified, mifepristone can be dispensed through a pharmacy, provided the product is prescribed by a certified prescriber and all other requirements of the REMS are met. Given this modification to the dispensing requirements in the REMS, it is necessary to add a requirement for certification of pharmacies under ETASU B. Adding the pharmacy certification requirement incorporates pharmacies into the REMS, ensures that pharmacies are aware of and agree to follow applicable REMS requirements, and ensures that mifepristone is only dispensed pursuant to prescriptions that are written by certified prescribers. Without pharmacy certification, a pharmacy might dispense product that was not prescribed by a certified prescriber. Adding pharmacy certification ensures that ETASU A is met prior to dispensing the product to a patient; certified prescribers, in turn, have agreed to meet all the conditions of the REMS, including ensuring that the *Patient Agreement Form* (ETASU D) is completed. In addition, wholesalers and distributors can only ship to certified pharmacies. Based on our review of the safety data and our consideration of the distribution model implemented by the Applicants during the periods

y ANDA 091178: September 23, 2021 response to the September 15, 2021 information request; October 11 and 16, 2021 responses to the June 30, 2021 and July 15, 2021 information requests; October 26, 2021 response to the October 22, 2021 information request; October 29, 2021 response to the October 27 information request.

z NDA 020687: September 20, 2021 response to the September 15, 2021 information request; October 26, 2021 response to the October 22 information request.

when the in-person dispensing requirement was not being enforced, as well as REMS assessment data and published literature, we conclude that provided all other requirements of the REMS are met, the REMS program, with the removal of the in-person dispensing requirement and the addition of a requirement for pharmacy certification, will continue to ensure the benefits of mifepristone for medical abortion outweigh the risks while minimizing the burden imposed by the REMS on healthcare providers and patients. As modified, the REMS would allow, for example, dispensing by mail order or specialty pharmacies, similar to the distribution model used by applicants during the periods when the in-person dispensing requirement was not being enforced.^{aa}

The above recommendations were discussed with the (b) (6) (b) (6) and senior leadership from CDER on November 2, 2021. The (b) (6) (b) (4) along with senior CDER leadership, concurred with removing the in-person dispensing requirement provided that all of the remaining REMS requirements are met, including but not limited to prescriber certification where prescribers need to attest to having certain qualifications, and maintaining the *Patient Agreement Form*. The (b) (6) (b) (4) and senior leadership from CDER were also in favor of adding pharmacy certification to assure the safe use of mifepristone.

5. Conclusions and Recommendations

Based on the results of REMS assessments; our review of safety data collected during the PHE as well as data from FAERS; our literature search; and information provided by advocacy groups, individuals, the Applicants, and the plaintiffs in the *Chelius v. Becerra* litigation, (b) (6) and (b) (6) have concluded that a REMS modification is necessary and should include the following changes:

- Removing the requirement under ETASU C that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals.
- Adding a requirement under ETASU B that pharmacies that dispense the drug be specially certified.

^{aa} Our current conclusion that the REMS would allow dispensing by mail order or specialty pharmacies is based on data received from Applicants relating to the periods when the in-person dispensing requirement was not enforced and mail-order pharmacies were used to dispense the product, as well as our analysis of postmarketing safety data and available literature. At this time we do not have data (from the Applicants or from other sources) to assess the certification of retail pharmacies under the REMS. We have not yet determined the details of pharmacy certification requirements, including whether any limitations on the types of pharmacies that may dispense the product are necessary.

(b) (6) and (b) (6) recommend the Applicants be issued a REMS Modification Notification Letter that requests submission within 120 days from the date of the letter.

6. References

¹ Grossman D, Raifman S, Morris N, et.al. Mail-order pharmacy dispensing of mifepristone for medication abortion after in-person clinical assessment. *Contraception* 2021; In press.
doi:<https://doi.org/10.1016/j.contraception.2021.09.008>

² Grossman D, Baba CF, Kaller S, et al. Medication Abortion With Pharmacist Dispensing of Mifepristone. *Obstet Gynecol* 2021;137:613–22.

³ Chong E, Shochet T, et al. Expansion of a direct-to-patient telemedicine abortion service in the United States and experience during the COVID-19 pandemic. *Contraception* 2021;104:43-48.

⁴ Kerestes C, Murayama S, et al. Provision of medication abortion in Hawai'i during COVID-19: Practical experience with multiple care delivery models. *Contraception* 2021 Jul;104(1):49-53.
doi:10.1016/j.contraception.2021.03.025. Epub 2021 Mar 28.

⁵ Aiken ARA, Lohr PA, et al. Effectiveness, safety and acceptability of no-test medical abortion (termination of pregnancy) provided via telemedicine: a national cohort study. *BJOG* 2021;128:1464–1474.

⁶ Rocca CH, Puri M, et al. Effectiveness and safety of early medication abortion provided in pharmacies by auxiliary nurse-midwives: A non-inferiority study in Nepal. *PLoS ONE* 2018 13(1): e0191174. <https://doi.org/10.1371/journal.pone.0191174>

⁷ Wiebe ER, Campbell M, et al. Comparing telemedicine to in-clinic medication abortions induced with mifepristone and misoprostol. *Contracept X*. 2020; 2: 100023.

⁸ National Abortion Federation 2020 Clinical Policy Guidelines for Abortion Care, available at https://5aa1b2xfmfh2e2mk03kk8rsx-wpengine.netdna-ssl.com/wp-content/uploads/2020_CPGs.pdf

⁹ American College of Obstetricians and Gynecologists Committee on Practice Bulletins—Gynecology and the Society of Family Planning. Simultaneously published as ACOG Bulletin

Number 225: Medication abortion up to 70 days of gestation. *Obstet Gynecol* 2020;136(4): e31-e47 and in *Contraception* 2020; 102:225-236.

¹⁰ Jones HE, O'Connell White K, Norman WV, Guilbert E, Lichtenberg ES, Paul M. First trimester medication abortion practice in the United States and Canada. *PLoS ONE* 2017; 12(10): e0186487. <https://doi.org/10.1371/journal.pone.0186487>

¹¹ Grossman D, Grindlay K, Altshuler AL, Schulkin J. Induced abortion provision among a national sample of obstetrician-gynecologists. *Obstet Gynecol* 2019;133:477-483.

¹² Daniel S, Schulkin J, Grossman D. Obstetrician-gynecologist willingness to provide medication abortion with removal of the in-person dispensing requirement for mifepristone. *Contraception*. 2021;104:73-76

¹³ (b) (6) Review of the one-year REMS assessment report for the Mifepristone REMS Program, December 16, 2021.

¹⁴ Upadhyay UD, Koenig LR, Meckstroth KR. Safety and Efficacy of Telehealth Medication Abortion in the US During the COVID-19 Pandemic. *JAMA Network Open*. 2021;4(8):e2122320. doi:10.1001/jamanetworkopen.2021.22320

¹⁵ Hyland P, Raymond EG, Chong E. A direct-to-patient telemedicine abortion service in Australia: Retrospective analysis of the first 18 months. *Aust N Z J Obstet Gynaecol* 2018;58: 335-340.

¹⁶ Raymond E, Chong E, et al. TelAbortion: evaluation of a direct to patient telemedicine abortion service in the United States. *Contraception* 2019;100:173-177

¹⁷ Anger HA, Raymond EG, et al. Clinical and service delivery implications of omitting ultrasound before medication abortion provided via direct-to-patient telemedicine and mail. *Contraception* 2021 Jul 28;S0010-7824(21)00342-5. doi: 10.1016/j.contraception.2021.07.108. Published online.

¹⁸ Reynolds-Wright JJ, Johnstone A, McCabe K, et al. Telemedicine medical abortion at home under 12 weeks' gestation: a prospective observational cohort study during the COVID-19 pandemic. *BMJ Sex Reprod Health* 2021;0:1–6. doi:10.1136/bmjsexrh-2020-200976

¹⁹ Aiken AR, Digon I, Trussell J, et al. Self reported outcomes and adverse events after medical abortion through online telemedicine: population based study in the Republic of Ireland and Northern Ireland. *BMJ* 2017;357:j2011.

²⁰ Norton H, Ilozumba O, Wilkinson J, et.al. 10-year evaluation of the use of medical abortion through telemedicine: a retrospective cohort study. *BJOG* 2021; <https://doi.org/10.1111/1471-0528.16765>.

²¹ Endler M, Beets L, Gemzell Danielsson K, Gomperts R. Safety and acceptability of medical abortion through telemedicine after 9 weeks of gestation: a population-based cohort study. *BJOG* 2019;126:609–618.

²² Raymond EG, Grossman D, Mark A, et.al. Commentary: No-test medication abortion: A sample protocol for increasing access during a pandemic and beyond. *Contraception* 2020;101:361-366

²³ Mark A, Foster A, Perritt J. The future of abortion is now: Mifepristone by mail and in-clinic abortion access in the United States. *Contraception* 2021;104:38-42

²⁴ Martin D, Miller A, Quesnel-Vallee, A, et al. Canada's global leadership on health 1. Canada's universal health care system: achieving its potential. *Lancet* 2018; 391:1718-35

7. Appendix A

References Cited in Letters from Plaintiffs

References cited in letter from <i>Chelius v. Becerra</i> Plaintiffs (September 29, 2021)	
References included in the REMS review	
Aiken A et al. BJOG 2021; 128 (9): 1464-1474	
Chong, et al. Contraception 2021; 104(1) 43-48	
Daniel S. et al. Contraception 2021; 104(1): 73-76	
References excluded from the REMS review	Rationale for Exclusion
Am. Coll. of Obstetricians & Gynecologists, <i>Position Statement: Improving Access to Mifepristone for Reproductive Health Indications</i> (June 2018), https://www.acog.org/clinical-information/policy-and-position-statements/position-statements/2018/improving-access-to-mifepristone-for-reproductive-health-indications	Policy/advocacy statement
House of Delegates, Am. Med. Ass'n., <i>Memorial Resolutions Adopted Unanimously No. 504 (2018)</i> https://www.ama-assn.org/sites/ama-assn.org/files/corp/media-browser/public/hod/a18-resolutions.pdf	Policy/advocacy statement
Cong. Of Delegates, Am. Acad. Of Fam. Physicians, <i>Resolution No. 506 (CoSponsored C) Removing Risk Evaluation and Mitigation Strategy (REMS) Categorization of Mifepristone</i> (May 24, 2018) https://www.reproductiveaccess.org/wp-content/uploads/2019/02/Resolution-No.-506-REMS.pdf	Policy/advocacy statement
Schummers L et al, Contraception 2020; 102(4): 273	Abstract
Upadhyay UD et al.) Obstet & Gynecol 2015; 125: 175	Published prior to March 29, 2016-July 26, 2021 timeframe for current literature review. We note that the extensive literature review conducted as part of the 2016 review, which was consistent with the division's standard approach for reviewing an efficacy supplement

	and encompassed 90 references, did not capture this publication. However, the authors' conclusion in this publication is consistent with our review of the safety data in 2016.
Kapp N et al. Best Pract Clin Obstet Gynaecol. 2020;63:37-44	Abstract. Also outside the scope of first trimester medical abortion.
<p>Fuentes L et al. J Women's Health 2019; 28 (12): 1623, 1625</p> <p>Bearak JM, Lancet Pub Health 2017 Nov;2(11): e493, e495-96</p> <p>Cartwright A et al 20 J Med Internet Res 2018 20(5):e10235</p> <p>Barr-Walker J, et al PLoS One 2019;14(4): e0209991</p> <p>Grossman et al JAMA Network 2017;317(4):437, 437-438</p> <p>Dobie S et al 31 Fam Plan Persp 1999; 31(5): 241-244</p> <p>Shelton JD 8 Fam Plan Persp 1976; 8(6):260, 260-262</p> <p>Norris AH et al Am J Pub Health 2020; 110 (8): 1228,1232</p> <p>Upadhyay UD et al Am J Pub Health 2014; 104(9):1687, 1689</p>	Focused on the logistics of accessing abortion care.
<p>CDC MMWR Abortion Surveillance – United States, 2018</p> <p>https://www.cdc.gov/mmwr/volumes/69/ss/ss6907a1.htm#T5 down</p>	Contains primarily general statistics on abortion care by state.

References cited in appendix from <i>Chelius v. Becerra</i> Plaintiffs (September 29, 2021)
References included in the REMS review
None

References excluded from the REMS review	Rationale for Exclusion
Jones RK et al Guttmacher Institute Abortion Incidence and Service Availability in the United States, 2017 (2019) Guttmacher Inst, Induced Abortion in the United States (2019)	Contains primarily general statistics on abortion care and logistics of accessing abortion care.
University of Minnesota Healthy Youth Dev. Prevention Rsch Ctr, 2019 Minnesota Adolescent Sexual Health Report 3 (2019)	Not related specifically to abortion care.
Jerman J et al Guttmacher Inst, Characteristics of U.S. Abortion Patients in 2014 and Changes since 2008 (2016)	Contains figures on patient characteristics from 2008-2014.
Roberts CM et al Women's Health Issues 2014; 24:e211, e215	Focused on cost of abortion.
CDC MMWR Abortion Surveillance 2018 https://www.cdc.gov/mmwr/volumes/69/ss/ss6907a1.htm#T7 down (last updated Nov. 7, 2020)	Contains primarily statistics on number of abortions in the US.
Jones RK Persp on Sexual & Reprod Health 2017; 49:17, 20	Focused on abortion incidence and service availability.
Fuentes L et al (as above) Bearak JM et al (as above) Cartwright A et al (as above) Johns NE et al. BMC Health Serv Res 2017; 17: 287, 294	Focused on logistics of accessing abortion care.

References cited in letter from Society of Family Planning (August 11, 2021)
References included in the REMS review
Grossman D. Obstet Gynecol 2019;133 (3): 477-483

Grossman D et al. Obstet Gynecol 2021; 137 (4): 613-622.	
Winikoff B et al. Obstet Gynecol 2012; 120: 1070-1076 reviewed in 2016 clinical memo	
Chen MJ et al. Obstet Gynecol 2015;126(1):12-21 reviewed in 2016 memo	
Chong et al. Contraception 2021;104(1): 43-48	
Aiken A et al. BJOG 2021; 128 (9): 1464 -1474	
Hyland 2018 et al. Aust New Zeal J Obstet Gynaecol 2018; 58 (3): 335-340	
References excluded from the REMS review	Rationale for Exclusion
Schummers L et al. BMJ Sex Reprod Heal 2021;47(e1)	Abstract
Kapp et al. 2020 (as above)	Abstract
Upadhyay et al. 2015 (as above)	(See rationale above)
Srinivasulu et al. Contraception 2021; 104(1):92-97	Survey on clinician perspectives on access to mifepristone.
Calloway D et al. Contraception 2021; 104(1): 24-28	Primarily addresses provider stigma around abortion care.
Rasmussen et al. Contraception; 104(1): 98-103	Opinion/commentary
Cleland et al. Obstet Gynecol 2013;121(1):166-171	Published prior to March 29, 2016 - July 26, 2021 timeframe for current literature review. We note that the extensive literature search conducted as part of the 2016 clinical review, which was consistent with the division's standard approach for reviewing an efficacy supplement and encompassed 90 references, did not capture this publication. However, the authors' conclusion in this publication is consistent with our review of the safety data in 2016.
National Academy of Sciences, Engineering, and Medicine. Safety and Quality of Abortion Care in the US 2018	General information about abortion care in the US. Did not provide safety data relevant to the elements of the REMS
Raymond EG. Obstet Gynecol 2012; 119(2): 215-219	Does not separate out medical and surgical abortion.

Bartlett LA et al. Obstet Gynecol 2004; 103(4): 729-737	Focused on surgical abortion.
Jones RK, Jerman J. Time to appointment and delays in accessing care among U.S. abortion patients, Guttmacher 2016	Focused on logistics of accessing abortion care.
Foster DG et al. Perspect Sex Reprod Health 2013; 45(4):210-218	Focused on second trimester abortion.
Ely G et al. Heal Soc Work 2019;44(1):13-21	Focused on logistics of accessing abortion care.
Munro S et al. Ann Fam Med 2020; 18(5):413-421.	Survey on physician perspectives on implementing medical abortion with mifepristone.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

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EXHIBIT D



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December 16, 2021

Re: Docket No. FDA-2019-P-1534

Dear Drs. Harrison and Van Meter:

This letter responds to your citizen petition submitted to the Food and Drug Administration (FDA or Agency) on March 29, 2019, on behalf of the American Association of Pro-Life Obstetricians and Gynecologists and the American College of Pediatricians (Petition). In the Petition, you request that FDA: (1) restore and strengthen elements of the Mifeprex regimen and prescriber requirements approved in 2000, and (2) retain the Mifeprex Risk Evaluation and Mitigation Strategy (REMS) and continue limiting the dispensing of Mifeprex to patients in clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber.

Specifically, in your Petition you request that the Agency:

- (1) Restore and strengthen elements of the Mifeprex regimen and prescriber requirements approved in 2000, to include the following:
 - Indications and Usage - Mifeprex, in a regimen with misoprostol, for the termination of intrauterine pregnancy, should be limited to 49 days gestation.
 - Dosage and Administration:
 - Mifeprex should be administered by or under the supervision of a physically present and certified physician who has ruled out ectopic pregnancy.
 - The use of Mifeprex and misoprostol for the termination of pregnancy should require three office visits by the patient.

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- Contraindications - Mifeprex use is contraindicated for patients who do not have convenient access to emergency medical care.
 - Adverse Event Reporting - Certified prescribers, emergency medical personnel, physicians treating complications, and Danco Laboratories should report to FDA's MedWatch Reporting system any deaths, hospitalizations, blood transfusions, emergency room visits, failures requiring surgical completion, ongoing pregnancy, or other major complications following the use of Mifeprex and misoprostol.
 - Additional studies - The Mifeprex REMS should require a formal study of outcomes for at-risk populations, including: patients under the age of 18; patients with repeat Mifeprex abortions; patients who have limited access to emergency room services; and patients who self-administer misoprostol.
- (2) Retain the Mifeprex REMS and continue limiting the dispensing of Mifeprex to patients in clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber.

We have carefully considered the information submitted in your Petition and other relevant data available to the Agency. Based on our review of this information, your Petition is granted in part and denied in part.

I. BACKGROUND

A. Mifeprex

On September 28, 2000, FDA approved Mifeprex for the medical termination of intrauterine pregnancy through 49 days' pregnancy (new drug application (NDA) 020687). The application was approved under part 314, subpart H (21 CFR part 314, subpart H), "Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses" (subpart H). Specifically, § 314.520 of subpart H provides for approval with restrictions that are needed to assure the safe use of the drug product. In accordance with § 314.520, FDA restricted the distribution of Mifeprex as specified in the September 2000 approval letter.¹

Subsequently, Mifeprex was identified as one of the products that was deemed to have in effect an approved REMS under the Food and Drug Administration Amendments Act of 2007 (FDAAA) because on the effective date of Title IX, subtitle A of FDAAA (March 28, 2008), Mifeprex had in effect elements to assure safe use.² Accordingly, in June 2011, we approved a REMS for Mifeprex, consisting of a Medication Guide, elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments of the REMS.

Elements to assure safe use included: (1) prescriber certification (ETASU A); (2) that Mifeprex is dispensed only in certain healthcare settings by or under the supervision of a certified prescriber

¹ See https://www.accessdata.fda.gov/drugsatfda_docs/appltr/2000/20687appltr.pdf.

² 73 FR 16313 (Mar. 27, 2008).

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(ETASU C); and (3) that Mifeprex is dispensed only with documentation of safe use conditions (ETASU D). Documentation of safe use conditions consists of a Patient Agreement Form between the prescriber and the patient indicating that the patient has received counseling from the prescriber regarding the risk of serious complications associated with Mifeprex.

On March 29, 2016, we approved an efficacy supplement (S-020) to NDA 020687 for Mifeprex submitted by the applicant Danco Laboratories, LLC (S-020 efficacy supplement). The approval included changes in the dose of Mifeprex and the dosing regimen for taking Mifeprex and misoprostol (including the dose of misoprostol and a change in the route of misoprostol administration from oral to buccal (in the cheek pouch); the interval between taking Mifeprex and misoprostol; and the location at which the patient may take misoprostol). The approval also modified the gestational age up to which Mifeprex has been shown to be safe and effective, as well as the process for follow-up after administration of the drug.

Specifically, the following changes, among others, were made as part of the 2016 approval:³

- Revised the dosing regimen to consist of 200 mg of Mifeprex taken by mouth, followed in 24-48 hours by 800 mcg of misoprostol taken buccally (in the cheek pouch). This differs from the originally approved dosing regimen of 600 mg of oral Mifeprex followed 48 hours later by 400 mcg of oral misoprostol.
- Revised the indication for use of Mifeprex, in a regimen with misoprostol, to extend the maximum gestational age for the medical termination of intrauterine pregnancy from 49 days to 70 days.
- Reduced the number of office visits by the patient under the approved regimen from three to one.
- Replaced the term “physician” with the term “healthcare provider.”

In addition, after reviewing the data and information submitted by the applicant in the S-020 efficacy supplement, and after taking into consideration the safety data that had become available since the initial approval of Mifeprex in 2000, we determined the Mifeprex REMS continued to be necessary to ensure the benefits of the product outweigh the risks. However, we approved modifications to the Mifeprex REMS that reflected the changes approved in the efficacy supplement. These changes to the REMS included, among others:⁴

- Updating the Prescriber Agreement Form to reflect the revised indication and dosing regimen.
- Removing the Medication Guide as a REMS element (but retaining the Medication Guide as labeling).

³ See https://www.accessdata.fda.gov/drugsatfda_docs/applletter/2016/020687Orig1s020ltr.pdf and https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf.

⁴ See https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020RemsR.pdf.

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- Removing the requirement that certified prescribers report certain enumerated adverse events to the applicant (specifically, any hospitalization, transfusion or other serious adverse events), but retaining the requirement that certified prescribers report all deaths to the sponsor.

Under the March 2016 approval, the Mifeprex REMS also continued to require that Mifeprex be dispensed to patients only in certain healthcare settings, specifically, clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber.⁵

B. Generic Version of Mifeprex

On April 11, 2019, we approved GenBioPro, Inc.'s generic version of Mifeprex, Mifepristone Tablets, 200 mg (abbreviated new drug application (ANDA) 091178). This action took place after this Petition was submitted to the Agency. As required by 21 CFR 314.94(a)(8), GenBioPro's approved generic version of Mifeprex, Mifepristone Tablets, 200 mg, has the same labeling (with certain permissible differences) as the brand product it references, Mifeprex. Accordingly, although we refer to the Mifeprex labeling in several sections of this response, our discussions in this response apply equally to both the NDA and the generic product labeling, unless otherwise specifically noted.⁶

GenBioPro's generic version of Mifeprex is subject to the same ETASU as its listed drug (21 U.S.C. -1(i)). At the time we approved GenBioPro's generic version of Mifeprex, that ANDA product was required to use a single, shared system for the ETASU with the brand drug product, Mifeprex, unless the requirement was waived by FDA (21 U.S.C. 355-1(i)). FDA did not waive this requirement. Accordingly, at the same time that FDA approved GenBioPro's generic version of Mifeprex in 2019, FDA approved a supplemental new drug application (sNDA) for Mifeprex, approving modifications to the existing, approved REMS for Mifeprex to establish a single, shared system REMS for mifepristone products for the medical termination of intrauterine pregnancy through 70 days gestation (referred to as the Mifepristone REMS Program). In establishing the single, shared system REMS in 2019, no substantive changes were made to the ETASU in the March 2016 Mifeprex REMS. References to the REMS in this response refer to the Mifepristone REMS Program established in 2019, unless otherwise noted.

C. In-Person Dispensing Requirement During the COVID-19 PHE

⁵ See https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2016/020687Orig1s020ltr.pdf.

⁶ We note that Korlym and the generic version of Korlym (Mifepristone Tablets, 300 mg) contain the same active ingredient – mifepristone – as Mifeprex and the generic version of Mifeprex (Mifepristone Tablets, 200 mg). Although these drug products contain the same active ingredient, their intended uses target different receptors, and the products have different strengths and use different dosing regimens. Korlym and the generic version of Korlym are approved for the control of hyperglycemia (high blood sugar levels) due to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes or glucose intolerance, and have failed surgery or are not candidates for surgery. References to mifepristone in this response refer to the use of mifepristone for the medical termination of intrauterine pregnancy through 70 days gestation, unless otherwise noted.

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FDA has recognized that during the COVID-19⁷ public health emergency (PHE),⁸ certain REMS requirements for various products may be difficult to comply with because patients may need to avoid public places and patients suspected of having COVID-19 may be self-isolating and/or subject to quarantine. The Agency has also received queries concerning products with REMS that have ETASUs, including REMS with ETASUs that restrict distribution, and the impact of such ETASUs on patient access when patients self-isolate or are subject to quarantine.

In April 2021, FDA communicated its intent to exercise enforcement discretion during the COVID-19 PHE regarding the requirement in the Mifepristone REMS Program that mifepristone used for medical termination of intrauterine pregnancy through 70 days gestation be dispensed to patients by or under the supervision of a certified prescriber only in certain healthcare settings, specifically clinics, medical offices, and hospitals (referred to as the “in-person dispensing requirement”).

Specifically, FDA communicated that provided all other requirements of the Mifepristone REMS Program are met, the Agency intends to exercise enforcement discretion with respect to the in-person dispensing requirement of the Mifepristone REMS Program, including any in-person requirements that may be related to the Patient Agreement Form, during the COVID-19 PHE. This determination, which FDA made on April 12, 2021, was effective immediately. We also note that from July 13, 2020 to January 12, 2021, per a court order, FDA was enjoined from enforcing the in-person dispensing requirement of the Mifepristone REMS Program.⁹

Further, and as we also communicated on April 12, 2021, to the extent all of the other requirements of the Mifepristone REMS Program are met, the Agency intends to exercise enforcement discretion during the COVID-19 PHE with respect to the dispensing of Mifeprex or the approved generic version of Mifeprex, Mifepristone Tablets, 200 mg, through the mail, either by or under the supervision of a certified prescriber, or through a mail-order pharmacy when such dispensing is done under the supervision of a certified prescriber.

FDA’s intent to exercise enforcement discretion with respect to these requirements during the COVID-19 PHE was the result of a thorough scientific review by experts within FDA’s Center for Drug Evaluation and Research (CDER), who evaluated relevant information, including available clinical outcomes data and adverse event reports.

D. Minor Modification

⁷ The virus has been named “SARS-CoV-2” and the disease it causes has been named “Coronavirus Disease 2019” (COVID-19).

⁸ Secretary of Health and Human Services, Determination that a Public Health Emergency Exists (originally issued Jan. 31, 2020, and subsequently renewed), *available at* <https://www.phe.gov/emergency/news/healthactions/phe/Pages/default.aspx>.

⁹ *Am. Coll. of Obstetricians & Gynecologists v. FDA*, 472 F. Supp. 3d 183, 233 (D. Md. July 13, 2020), order clarified, 2020 WL 8167535 (D. Md. Aug. 19, 2020) (preliminarily enjoining FDA from enforcing the in-person dispensing requirement and any other in-person requirements of the Mifepristone SSS REMS); *FDA v. Am. Coll. of Obstetricians & Gynecologists*, 141 S. Ct. 578 (Jan. 12, 2021) (staying the preliminary injunction imposed by the District Court).

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In response to a request submitted by the applicants, FDA approved a minor modification to the Mifepristone REMS Program on May 14, 2021. This minor modification revised the Patient Agreement Form to use gender neutral language. Specifically, the pronouns “she” and “her” in the Patient Agreement Form were replaced with “the patient.” The minor modification also included revisions to the REMS document to be consistent with the revisions to the Patient Agreement Form. These changes did not affect the substance of the Patient Agreement Form, the REMS document, or the Mifepristone REMS Program.

E. Review of the Mifepristone REMS Program

In 2021, FDA also undertook a full review of the Mifepristone REMS Program.¹⁰ In conducting this review, FDA reviewed multiple different sources of information, including published literature, safety information submitted to the Agency during the COVID-19 PHE, FDA Adverse Event Reporting System (FAERS) reports, the first REMS assessment report for the Mifepristone REMS Program, and information provided by advocacy groups, individuals, and the Plaintiffs in ongoing litigation, as well as information submitted by the sponsors of the NDA and the ANDA (together, the Applicants). As discussed in more detail below, based on our review of this information, FDA has determined that certain elements of the Mifepristone REMS Program remain necessary to assure the safe use of mifepristone for medical termination of intrauterine pregnancy through 70 days gestation; and therefore, the Mifepristone REMS Program continues to be necessary to ensure the benefits outweigh the risk. Specifically, we find that the healthcare provider certification and dispensing of mifepristone to patients with evidence or other documentation of safe use conditions continue to be necessary components of the REMS to ensure the benefits of mifepristone outweigh the risks for this indication.

We also find that the in-person dispensing requirement is no longer necessary to assure the safe use of mifepristone for medical termination of intrauterine pregnancy through 70 days gestation. We have concluded that mifepristone will remain safe and effective for medical abortion if the in-person dispensing requirement is removed, provided all the other requirements of the REMS are met and pharmacy certification is added.¹¹ Removing the in-person dispensing requirement will render the REMS less burdensome to healthcare providers and patients, and provided all other requirements of the REMS are met, including the additional requirement for pharmacy certification, the REMS will continue to ensure that the benefits of mifepristone for medical abortion outweigh the risks. Accordingly, today we are sending a REMS Modification Notification letter to both Applicants in the Mifepristone REMS Program. As stated in that letter, FDA has concluded that a modification is necessary and must include the following changes:

- Removing the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals.

¹⁰ We note that the Agency is in litigation regarding the Mifepristone REMS Program and committed to conducting a full review of the Mifepristone REMS Program, including reviewing any relevant data and evidence submitted to the Agency by the Plaintiffs in that litigation (*Chelius et al v. Becerra*, Joint Mot. to Stay Case Pending Agency Review, ECF No. 148, May 7, 2021, Civ. No. 1:17-00493 (D. Haw.)).

¹¹ Although we have determined that the Mifepristone REMS Program must be modified to add a requirement for pharmacy certification, this was not raised in your Petition and therefore is not discussed further in this response.

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- Adding a requirement that pharmacies that dispense the drug be specially certified.

II. DISCUSSION OF ISSUES RAISED

A. Mifeprax Regimen

1. Indications and Usage

In the Petition, you ask FDA to restore and strengthen elements of the Mifeprax regimen and prescriber requirements approved in 2000, to limit Mifeprax, in a regimen with misoprostol, for the termination of intrauterine pregnancy, to 49 days gestation (Petition at 1 and 3). For the reasons explained below, we deny this request.

Citing to a 2011 study and a practice bulletin issued by the American College of Obstetricians and Gynecologists (ACOG), you state that medical abortion¹² regimens demonstrate an increase in complications and failures, including serious risks of hemorrhage, infection, and ongoing pregnancy, after 49 days gestation (Petition at 3-4).

Our review of the S-020 efficacy supplement in 2016 concluded that Mifeprax, in a regimen with misoprostol, is safe and effective for medical termination of intrauterine pregnancy through 70 days gestation.¹³ Complete medical abortion rates from the pivotal clinical trials relied on for the initial approval of Mifeprax (with an indication for medical termination of intrauterine pregnancy through 49 days gestation) were 92.1 percent and 95.5 percent in the United States and French trials, respectively.¹⁴ The studies reviewed in support of the 2016 approval for Mifeprax (with an indication for medical termination of intrauterine pregnancy through 70 days gestation) showed comparable efficacy. The 2016 Clinical Review of the S-020 efficacy supplement summarized clinical outcomes and adverse effects from 22 studies (7 in the United States and 15 from outside the United States) through 70 days gestation, using the currently approved regimen of 200 mg oral mifepristone with 800 mcg buccal misoprostol. The ranges of complete medical abortion rates calculated by the clinical reviewer were 93.2 percent to 98.7 percent in the United States studies, and 92 percent to 98 percent in the non-United States studies.¹⁵

Serious adverse events associated with the use of mifepristone through 70 days gestational age are rare. Per the current mifepristone labeling, the rates of serious adverse events are low: transfusions are 0-0.1 percent, sepsis is less than 0.01 percent, hospitalization related to medical abortion is 0-0.7 percent, and hemorrhage is 0.1 percent.¹⁶ As discussed

¹² In this response, the terms “medical abortion” and “medication abortion” both refer to the use of mifepristone, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy.

¹³ See 2016 Clinical Review available at

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020MedR.pdf, at 32-38 and 47-47.

¹⁴ See 1999 Medical Officer’s Review, available at

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_medr_P1.pdf, at 11 (Table 1) and 16.

¹⁵ See 2016 Clinical Review, *supra* n. 13, at 28-31.

¹⁶ See https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf.

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throughout this response, the benefit/risk assessment supported our 2016 conclusion that the product is safe and effective through 70 days gestation.

In support of your assertion that medical abortion demonstrates an increase in complications after 49 days gestation, you cite to Mentula, et al.,¹⁷ a register-based, retrospective cohort study that included 18,248 women in Finland who underwent medical abortion between January 1, 2003, and December 31, 2006 (Petition at 3). As an initial matter, we note that the Mentula study was primarily designed to assess the immediate adverse events following medical abortion in the second trimester (13 to 24 gestational weeks as defined by the authors) and then compare those events to those identified with medical abortion in the first trimester (up to 12 gestational weeks as defined by the authors). The study was not designed to compare rates of complications across gestational weeks within the first trimester. It is true that the Mentula publication includes information on the percentages of women who had surgical evacuation following medical abortion and the percentages of women who had infection following medical abortion, based on weekly gestational age, from 5 weeks to 20 weeks gestation.¹⁸ However, the data in the Mentula study are relatively old (2003-2006); in our 2016 review of the S-020 efficacy supplement, we conducted an extensive review of more recent data¹⁹ and concluded that Mifeprex, in a regimen with misoprostol, is safe and effective for medical termination of intrauterine pregnancy through 70 days gestation.

You also cite to ACOG Practice Bulletin No. 143, which states: “the risk of clinically significant bleeding and transfusion may be lower in women who undergo medical abortion of gestations up to 49 days compared with those who undergo medical abortion of gestations of more than 49 days.”²⁰ This statement is based on a 1998 publication which evaluated patients undergoing medical abortion with mifepristone 600 mg and then oral misoprostol 400 mcg two days later.²¹ The regimen studied in this 1998 publication is not the currently approved regimen for mifepristone in the United States. Further, ACOG Practice Bulletin No. 143 has been withdrawn and replaced by Practice Bulletin No. 225, which was published in October 2020 and no longer contains this statement.²²

You also state that the failure rate of the approved regimen (which you refer to as the “buccal misoprostol regimen”) increases as the gestational age increases, especially at

¹⁷ Mentula MJ, Niinimäke M, Suhonen S, et al. Immediate Adverse Events After Second Trimester Medical Termination of Pregnancy: Results of a nationwide registry study, *Human Reproduction*. 2011;26(4):927-932.

¹⁸ *Id.* at Fig. 2 and Fig. 3. Surgical intervention after medical abortion and infection after medical abortion are two distinct adverse events. The calculation of abortion completion rates accounts for the need for surgical intervention. In clinical studies we reviewed, success of medical abortion was defined as the complete expulsion of the products of conception without the need for surgical intervention.

¹⁹ See 2016 Cross-Discipline Team Leader Review, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020CrossR.pdf, at 37 (Table 4).

²⁰ Petition at 3. See Medical Management of First-Trimester Abortion. ACOG Practice Bulletin Number 143. March 2014 (Reaffirmed 2016. Replaces Practice Bulletin Number 67, October 2005); *Obstet Gynecol*. 2014 Mar;123(3):676-692 at 680.

²¹ Spitz I, Bardin CW, Benton L, Robbins A. Early pregnancy termination with mifepristone and misoprostol in the United States, *NEJM*. 1998;338 (18):1241-1247.

²² See ACOG Practice Bulletin No. 225. Medication Abortion Up to 70 Days of Gestation. *Obstetrics and Gynecology* 2020; 136(4); e31 to e47.

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gestational ages greater than 49 days, relying on a 2015 meta-analysis,²³ and that the gestational limit should not have been increased (Petition at 3-4). We agree that the failure rate of medical abortion regimens, including the currently approved regimen, generally increases with increasing gestational age. However, the increase in failure rate with each incremental week of gestation, as described in approved mifepristone labeling and in this 2015 meta-analysis, is small, and we believe that the benefit/risk profile for medical termination of intrauterine pregnancy between 49 and 70 days gestation remains acceptable.

For these reasons, we deny your request that FDA limit mifepristone, in a regimen with misoprostol for the termination of intrauterine pregnancy, to 49 days gestation.

2. Dosage and Administration

a. Prescriber Qualifications

You state that FDA should limit the “ability” to prescribe and dispense Mifeprex to qualified, licensed physicians, rather than permitting non-physicians to apply to be certified prescribers, because of the regimen’s serious risks and because physicians are better trained to diagnose patients who have contraindications to Mifeprex and to verify gestational age (Petition at 4). We do not agree.

Healthcare providers who are licensed to prescribe can become certified in REMS programs if they are able to meet the applicable REMS requirements. To become certified to prescribe mifepristone under the Mifepristone REMS Program, the prescriber must review the prescribing information for mifepristone and complete a Prescriber Agreement Form. By signing the form, the prescriber agrees that they meet certain qualifications, including the ability to date pregnancies accurately and to diagnose ectopic pregnancies. These healthcare providers must also: (1) be able to provide any necessary surgical intervention or have made arrangements for others to provide for such care; or (2) be able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.²⁴

In our review of the S-020 efficacy supplement in 2016, we determined that available data support that Mifeprex is safe and effective when prescribed by midlevel providers, such as physician assistants and nurse practitioners, as well as by physicians.²⁵ Our 2016 review included four studies that evaluated the safety and efficacy of medical abortion when performed by non-physician healthcare providers. Two trials evaluated the currently

²³ Petition at 4, fn. 6 (citing Chen MJ, Creinin MD, *Mifepristone with Buccal Misoprostol for Medical Abortion*, *Obstet. Gynecol* 126 (1) July 2015 12-21).

²⁴ See https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s0221bl.pdf; see also <https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm?event=RemsDetails.page&REMS=390>.

²⁵ See 2016 Clinical Review, *supra* n. 13, at 79; see also 2016 Cross-Discipline Team Leader Review, *supra* n. 19, at 17-18. We also note that in most states, midlevel clinicians, such as physician assistants and nurse practitioners, are licensed to prescribe medications.

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approved Mifeprex and buccal misoprostol regimen (Olavarrieta and Kopp Kallner);^{26,27} one trial studied a regimen using vaginal misoprostol (Warringer);²⁸ a fourth study did not specify the route of misoprostol administered (Puri).²⁹ Olavarrieta reported a completion rate of 97.9 percent when medical abortion was provided by nurses as compared with 98.4 percent with physicians. Kopp Kallner reported a completion rate of 99 percent with certified nurse midwives versus 97.4 percent with physicians. Warringer reported an abortion completion rate of 97.4 percent with nurses as compared with 96.3 percent with physicians. Puri reported an abortion completion rate of 96.8 percent when the service was provided by nurse-midwives as compared with 97.4 percent in the “standard care” group.³⁰ Our 2016 review also included a systematic review of six controlled clinical studies by Renner;³¹ the authors concluded that the evidence “indicates that trained mid-level providers may effectively and safely provide first trimester surgical and medical termination of pregnancy services.” Additionally, Barnard et al., in a Cochrane systematic review, assessed the safety and effectiveness of abortion procedures administered by mid-level providers (nurse practitioners, midwives, other non-physician healthcare providers) compared to doctors.³² The authors concluded, based in part on two of the studies that we had reviewed in 2016,³³ that there was no statistically significant difference in the risk of failure for medical abortions performed by mid-level providers compared with doctors.

We also believe that the identification of patients for whom the use of mifepristone is contraindicated can be done by mid-level healthcare providers, as well as physicians. Mifepristone in a regimen with misoprostol for medical termination of intrauterine pregnancy through 70 days gestation is contraindicated in patients with any of the following conditions:³⁴

- Confirmed or suspected ectopic pregnancy or undiagnosed adnexal mass

²⁶ Olavarrieta CD, Ganatra B, Sorhaindo A, et al. Nurse versus Physician-provision of Early Medical Abortion in Mexico: A Randomized Controlled Non-Inferiority Trial. *Bull World Health Organ.* 2015;93:249-258.

²⁷ Kopp Kallner H, Gomperts R, Salomonsson E, et al. The efficacy, safety and acceptability of medical termination of pregnancy provided by standard care by doctors or by nurse-midwives: a randomised controlled equivalence trial. *BJOG.* 2015; 122: 510-517.

²⁸ Warriner IK, Wang D, et al. Can midlevel health-care providers administer early medical abortion as safely and effectively as doctors? A randomized controlled equivalence trial in Nepal. *Lancet.* 2011; 377: 1155-61.

²⁹ Puri M, Tamang A, Shrestha P, et al. The role of auxiliary nurse-midwives and community health volunteers in expanding access to medical abortion in rural Nepal. *Reproductive Health Matters.* 2015; 22(44) 94-103.

³⁰ 2016 Clinical Review, supra n. 13, at 43.

³¹ Renner RM, Brahmi D, Kapp N. Who can provide effective and safe termination of pregnancy care? A systematic review. *BJOG* 2013 Jan;120(1):23-31.

³² Barnard S, Kim C, Park MN, Ngo TD. Doctors or mid-level providers for abortion (Review). *Cochran Database of Systematic Reviews.* 2015, Issue 7.

³³ Of the medical abortion studies reviewed by Barnard et al (Id.), two were reviewed by the Agency as part of the review of the S-020 supplement in 2016. See Warriner et al (supra n. 28) and Kopp Kallner et al (supra n. 27). The third used a different dose of misoprostol than the currently approved regimen. See Jejeebhoy SJ, Kalyanwalaa S, Zaviera AJF, Kumara R, Mundle S, Tankc J, et al. Feasibility of expanding the medication abortion provider based in India to include ayurvedic physicians and nurses. *International Perspectives on Sexual and Reproductive Health* 2012;38(3)133-42)

³⁴ See https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf.

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- An intrauterine device in place
- Chronic adrenal failure
- Concurrent long-term corticosteroid therapy
- History of allergy to mifepristone, misoprostol, or other prostaglandins
- Hemorrhagic disorder or concurrent anticoagulant therapy
- Inherited porphyrias

These contraindications can be assessed by trained healthcare providers who prescribe mifepristone by obtaining a medical history, from medical records, and/or from physical examination or ultrasound if appropriate. We continue to believe that available data support the conclusion that mid-level healthcare providers, as well as physicians, possess the clinical and counseling skills necessary to provide medical abortion. We note this is consistent with ACOG's statement in its current practice bulletin that "[i]n addition to physicians, advanced practice clinicians, such as nurse-midwives, physician assistants, and nurse practitioners, possess the clinical and counseling skills necessary to provide first-trimester medical abortion."³⁵ Further, if necessary, ultrasound training and certification is available to nurse practitioners and physician assistants, as well as physicians.³⁶ In sum, available information supports that mid-level healthcare providers as well as physicians can determine whether mifepristone is an appropriate treatment for a particular patient and dispense it.

You also assert that FDA should strengthen the requirement that providers accurately assess the duration of the pregnancy by mandating that gestational age be assessed by ultrasound (Petition at 5). We refer you to FDA's 2016 Response to the citizen petition submitted to Docket No. FDA-2002-P-0364 (the "2016 CP Response"), where FDA stated that the determination of gestational age does not always require an ultrasound. In the 2016 CP Response, FDA stated it had "determined that it was inappropriate for us to mandate how providers clinically assess women for duration of pregnancy and for ectopic pregnancy. These decisions should be left to the professional judgment of each provider, as no method (including TVS [transvaginal ultrasound]) provides complete accuracy. The approved labeling for Mifeprex recommended ultrasound evaluation as needed, leaving this decision to the judgment of the provider."³⁷

In the Petition, you reference the Prescriber Agreement Form, in which the provider must attest they have the ability to: (1) accurately assess the duration of the pregnancy; (2) diagnose ectopic pregnancies; and (3) provide surgical intervention if needed (or have made plans to provide such care through others), and you state that a provider who does not physically meet with and examine a patient, but simply consults with the patient over the Internet, is not capable of fulfilling these requirements, or of ruling out additional

³⁵ ACOG Practice Bulletin No. 225, *supra* n. 22.

³⁶ American Institute of Ultrasound in Medicine. Accessed November 26, 2021. <https://www.aium.org/officialStatements/70>.

³⁷ FDA's citizen petition response dated March 29, 2016, to the citizen petition submitted by the American Association of Pro-Life Obstetricians and Gynecologists, the Christian Medical and Dental Association, and Concerned Women for America on August 20, 2002, Docket No. FDA-2002-P-0364 at 18. See <https://www.regulations.gov/document/FDA-2002-P-0364-0002>.

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contraindications (Petition at 5-6). You state that FDA should require certified prescribers to be physically present when Mifeprex is dispensed so that they can appropriately examine patients and rule out contraindications to the use of Mifeprex (Petition at 4).

Certified prescribers do not have to be physically present with the patient as long as they have confirmed the patient's gestational age and intrauterine pregnancy. As noted above, in the 2016 CP response, FDA "determined that it was inappropriate for us to mandate how providers clinically assess women for duration of pregnancy and for ectopic pregnancy."³⁸ Moreover, the evaluation of patients for contraindications to medical abortion does not necessarily require direct physical contact with the certified prescriber and can be done in different types of healthcare settings. A certified prescriber can also review the Patient Agreement Form³⁹ with the patient, fully explain the risks of the mifepristone treatment regimen, and answer any questions, as in any consent process, without physical proximity. See also section II.B.1.c (ETASU C – In-person Dispensing).

With respect to providing surgical intervention in cases of incomplete abortion or severe bleeding and assuring patient access to medical facilities equipped to provide blood transfusions and resuscitation (if necessary), the Prescriber Agreement Form does not reflect a requirement that the certified prescriber must provide such care personally; rather, the prescriber must agree that they have the ability to provide such care or that they have made plans to provide such care through others, and that they have the ability to assure the patient has access to appropriate medical facilities. It is common practice for healthcare providers to provide emergency care coverage for other healthcare providers' patients, and in many places, hospitals employ "hospitalists" to provide care to all hospitalized patients. We also note ACOG's statement that "[i]n rare cases, a patient who undergoes a medication abortion may need to obtain an additional intervention, such as uterine aspiration. If the prescribing clinician does not perform the intervention, it is medically appropriate to provide a referral."⁴⁰

For these reasons, we deny your request that FDA limit the "ability" to prescribe and dispense mifepristone to licensed physicians, and we deny your request that FDA require certified providers to physically meet with and examine the patient.

b. Office Visits and Administration of Mifepristone/Misoprostol

In the Petition, you state that the use of mifepristone and misoprostol should require three office visits by the patient (Petition at 7). In support of this position, you state the following:

- Drug-induced abortion is contraindicated for patients who are not available for follow-up contact or evaluation (Petition at 10).

³⁸ Id.

³⁹ See <https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm?event=RemsDetails.page&REMS=390>.

⁴⁰ ACOG Practice Bulletin Number 225 supra n. 22.

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- Abortion complications are more frequent when women abort at home and more healthcare oversight is needed (Petition at 8).
- Home administration of misoprostol does not permit healthcare providers to control when their patients take misoprostol and without monitoring:
 - a patient may take buccal misoprostol before the minimum 24-hour period after taking Mifeprex, which leads to a significantly increased failure rate (Petition at 7).
 - a patient may swallow misoprostol rather than administer it buccally, and oral administration is not as effective as buccal administration in ending the pregnancy (Petition at 7).
- Because providers may now “confirm” that a patient’s drug-induced abortion was successful without a clinic visit, this increases the threat that Rh-negative patients will not receive Rhogam, which is necessary to prevent serious risks in subsequent pregnancies (Petition at 7 and 9).

We address each of these points below.

i. Follow-up Care

The safe use of mifepristone when used in the approved regimen with misoprostol is not contingent on a specific number of office visits being made by the patient undergoing a medical termination of pregnancy. The 2016 labeling change for Mifeprex regarding post-treatment assessment, including the change to the approved regimen to reduce the number of offices visits from three to one, was based on evidence reviewed in the S-020 efficacy supplement. We concluded, upon reviewing the data, that three office visits were not necessary to assure the safe use of Mifeprex.⁴¹

In your Petition, you point to statements by ACOG that medical abortion is contraindicated for patients who are not available for follow-up contact or evaluation (Petition at 8, 10). The ACOG statements you point to are from ACOG Practice Bulletin No. 143, which has been withdrawn and replaced by Practice Bulletin No. 225.⁴² Neither of the statements from the withdrawn Practice Bulletin nor Practice Bulletin No. 225 contraindicate medical abortion in women who are not available for an in-clinic follow-up visit. The current ACOG recommendations indicate that for medical abortion, “[f]ollow-up can be performed by telephone at 1 week, with subsequent at-home urine pregnancy testing at 4 weeks after treatment, which avoids the need for the patient to go to a facility.”⁴³ The patient and their healthcare provider should determine the best option for follow-up as part of the consultation and consent process.⁴⁴ As reflected in ACOG’s guidance, appropriate follow-

⁴¹ See 2016 Clinical Review, *supra* n. 13, at 44 and 64-67.

⁴² ACOG Practice Bulletin Number 225, *supra* n. 22.

⁴³ *Id.*

⁴⁴ *Id.*

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up after medical termination of a pregnancy may be accomplished in multiple ways and not all require an in-clinic visit.

You also question findings in multiple studies that evaluated the effectiveness of semiquantitative urine pregnancy tests (multi-level pregnancy tests, or MLPT) and low sensitivity urine pregnancy tests (LSPT) to rule out on-going pregnancies and assessed the ability of patients to self-administer these tests and interpret the test results (Petition at 9-10). Overall, these studies concluded that in the majority of women, it is feasible to use a simplified test to determine if further follow-up is necessary. A recent systematic review and meta-analysis by Baiju assessed the effectiveness and safety of self-assessment of the outcome of medical abortion completed at home versus routine clinic follow-up after medical abortion, concluding self-assessment was not inferior to routine clinic follow-up.⁴⁵ We note that this is consistent with current ACOG recommendations, which state that “follow-up can be performed by telephone at 1 week, with subsequent at-home urine pregnancy testing at 4 weeks after treatment, which avoids the need for the patient to go to a facility.”⁴⁶

You also assert that it is important for a patient to be under observation after taking misoprostol to ensure that they are appropriately monitored and provided sufficient pain medication (Petition at 8). You cite the World Health Organization (WHO)’s statement in guidance that up to 90 percent of women will abort within 4-6 hours after taking misoprostol; you further state that the 2000 regimen permitted patients to be in the clinic during this time period (Petition at 8). Your reference to the WHO guidance document⁴⁷ appears to be out of context. The WHO guidance takes no position on whether women should return to and remain in the clinic during a follow-up visit for purposes of taking misoprostol; in fact, it explicitly recognizes that post-abortion care may not require a follow-up visit if the patient is adequately counseled.⁴⁸ In the United States, and as reflected in the approved labeling, medical termination of pregnancy usually involves patients terminating the pregnancy at home, with appropriate follow-up that may not include a return visit.

ii. At Home Medical Abortion and Healthcare Oversight

In addition, you cite a 2018 study to support your statement that abortion complications are more frequent when women abort at home (Petition at 8). The study evaluated complications following medical abortion (both less than 12 weeks and more than 12 weeks gestation) as well as following surgical abortion, at one hospital in Sweden between 2008 and 2015.⁴⁹ For the years 2008 to 2010, data were collected retrospectively; for the years

⁴⁵ Baiju, N, Acharya, G, D’Antonio, F, et al. 2019. Effectiveness, safety and acceptability of self-assessment of the outcome of first-trimester medical abortion: a systematic review and meta-analysis. BJOG; 126:1536-1544.

⁴⁶ ACOG Practice Bulletin Number 225, supra n. 22.

⁴⁷ World Health Organization, Safe Abortion: technical and policy guidance for health systems – 2nd edition. 2012. Page 45 and Section 2.2.2.1 Medication for pain.

⁴⁸ Id. at Section 2.3 Post-abortion care and follow-up, at 52.

⁴⁹ Carlsson I, Breiding K, Larsson PG, 2018, Complications Related to Induced Abortion: A Combined Retrospective and Longitudinal Follow-up Study, BMC Women’s Health 18:158.

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2011 to 2015, data were collected prospectively. In this study, medical abortions after 12 gestational weeks all occurred at the hospital. The authors report that, among medical abortions less than 12 weeks, the complication frequency increased from 5.4 percent (2008 to 2010) to 8.2 percent (2015). However, the authors also compared the complications related to medical abortions that occurred at less than 12 gestational weeks between “at home” abortions (managed as an outpatient) and “at the hospital” abortions, in 2015 and found no statistically significant difference (8.2 percent “at home” versus 8.0 percent at the hospital). For pregnancies less than or equal to 9 gestational weeks, the rates are similar for the “at home” group (10.0 percent) and the “at the hospital” group (9.3 percent). Notably, as part of our review and approval of the S-020 efficacy supplement in 2016, we assessed serious adverse events by gestational age, including hospitalizations, serious infection requiring hospitalization or intravenous antibiotics, bleeding requiring transfusion, and ectopic pregnancy, as reported in the literature submitted by the Applicant. We concluded that these serious adverse events are rarely reported in the literature and that the regimen of mifepristone 200 mg followed by buccal misoprostol 800 mcg in 24-48 hours is safe to approve for use through 70 days gestation.⁵⁰

You also state that medical abortion is a longer process than surgical abortion and that it requires more attention and care from healthcare providers (Petition at 10). We agree that medical abortion can be a longer process than surgical abortion,⁵¹ but we disagree that medical abortion always requires in-person follow-up with a healthcare provider. Not all of the complications associated with medical abortion necessarily require more intensive management from healthcare providers during a follow-up visit. The question of whether to include an in-person follow-up visit should be discussed by the healthcare provider and the patient. We have concluded that medical abortions are safe and effective for patients who are appropriate candidates and reducing the number of clinic visits does not compromise patient safety.

The current approved labeling for mifepristone for medical termination of pregnancy states that complete pregnancy termination “can be confirmed by medical history, clinical examination, human Chorionic Gonadotropin (hCG) testing, or ultrasonographic scan.” Not all these modalities require an in-clinic assessment during a follow-up visit. Our review of the S-020 efficacy supplement concluded that “available data support ... that there are a variety of follow-up modalities that can adequately identify the need for additional intervention.”⁵² We note that these findings are also consistent with ACOG guidelines, which state that “[r]outine in-person follow-up is not necessary after uncomplicated medication abortion” and recommend several methods for post-treatment follow-up, as appropriate, including serial serum hCG testing alone or telephone follow-up at one week after treatment followed by urine pregnancy testing at four weeks after treatment.⁵³ Because there is more than one effective method to detect an on-going pregnancy, we conclude that the way in which post-treatment follow-up is performed may be determined by the healthcare provider and the patient.

⁵⁰ 2016 Clinical Review, supra n. 13, at 51-57.

⁵¹ See ACOG Practice Bulletin Number 225, supra note 22.

⁵² 2016 Cross Discipline Team Leader Review, supra n. 19, at 17.

⁵³ ACOG Practice Bulletin Number 225, supra note 22.

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iii. Misoprostol

In the Petition, you make a number of assertions regarding the use of misoprostol. We address each in turn.

First, you assert that a patient may take misoprostol before the prescribed minimum 24-hour period after taking Mifeprex, thereby rendering the regimen ineffective, and that home administration of misoprostol does not permit health providers to control when their patients take misoprostol (Petition at 7). You similarly assert that the use of buccal misoprostol sooner than 24 hours after administering mifepristone leads to significantly increased failure rates (Petition at 7).

As an initial matter, our review of the S-020 efficacy supplement in 2016 included data that evaluated the home use of misoprostol in over 30,000 women. The data showed that Mifeprex was safe and effective in a regimen with misoprostol when misoprostol was self-administered at home.⁵⁴ Therefore, any incorrect administration resulting in a failed abortion was infrequent and did not significantly affect the safety and efficacy of medical abortion. Furthermore, because the process of expelling the pregnancy may begin as soon as 2 hours after taking misoprostol, there is a benefit in allowing patients to choose when and where to start this process, to maximize the possibility of their being at a safe place at a convenient time to experience cramping and bleeding.⁵⁵

In support of your assertion of significantly increased failure rates, you cite a pilot study by Lohr et al.⁵⁶ Lohr et al. assessed the complete abortion rate using simultaneous oral mifepristone and buccal misoprostol in three gestational age groupings (less than or equal to 49 days, 50-56 days, 57-63 days) and compared the rates with those published in previous pilot investigations⁵⁷ using simultaneous oral mifepristone and vaginal misoprostol in the same three gestational age groupings. The complete abortion rates reported by Lohr at 24 hours for oral mifepristone and buccal misoprostol were 72.5 percent, 69.2 percent, and 72.5 percent, respectively; the complete abortion rates at two weeks, however, were 97.5 percent, 100 percent, and 94.9 percent, respectively (and are consistent with the completion rates as described in the approved labeling).⁵⁸ The published complete abortion rates at 24 hours for simultaneous oral mifepristone and vaginal misoprostol administration were 90 percent, 88 percent, and 83 percent, respectively, for the gestational age groupings and the complete abortion rates at 2 weeks were 98 percent, 93 percent, 90 percent, respectively. Based on the data presented in Lohr,

⁵⁴ See 2016 Clinical Review, *supra* n. 13, at 41 and 48.

⁵⁵ *Id.* at 38.

⁵⁶ Petition at 7 (referencing Lohr PA, Reeves MF, Hayes JL, et al., 2007, Oral Mifepristone and Buccal Misoprostol Administered Simultaneously for Abortion: A Pilot Study, *Contraception*, 76:215-220).

⁵⁷ Schreiber CA, Creinin MD, Harwood B, Murthy AS. A pilot study of mifepristone and misoprostol administered at the same time for abortion in women with gestation from 50 to 63 days. *Contraception* 2005;71:447-50; Murthy AS, Creinin MD, Harwood B, Schreiber C. A pilot study of mifepristone and misoprostol administered at the same time for abortion up to 49 days gestation. *Contraception* 2005;71:333-6.

⁵⁸ See https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf.

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the use of buccal misoprostol at the same time as oral mifepristone does not adversely affect efficacy, although expulsion may be delayed. As recommended in Section 2.3 of the approved labeling, follow-up at 7-14 days after administration of mifepristone is more appropriate to evaluate efficacy.⁵⁹ It is misleading to only reference the abortion completion rates observed at the 24-hour timepoint from Lohr. Therefore, we do not agree that data from Lohr indicate higher failure rate with misoprostol taken before the prescribed minimum 24-hour period after taking mifepristone.

Although we disagree that Lohr demonstrates a higher failure rate with misoprostol taken before 24-hours after taking mifepristone, we note that our 2016 review of the S-020 efficacy supplement referenced a 2013 systematic review by Raymond, which concluded that if the interval between mifepristone and misoprostol interval is less than or equal to 24 hours, the procedure is less effective compared to an interval of 24-48 hours.⁶⁰ As explained above, the data reviewed in 2016 showed that Mifeprex, in a regimen with misoprostol administered at home, was safe and effective. Therefore, incorrect administration, if it occurred, was infrequent and did not significantly affect the safety and efficacy of medical abortion. However, in light of the data reviewed, section 2.1 of the labeling approved in 2016 (as well as the currently approved labeling and Medication Guide) states that there should be a “minimum 24-hour interval between” mifepristone and misoprostol (emphasis included in the labeling).⁶¹ The approved dosing regimen also states that misoprostol is taken within 24 to 48 hours after taking mifepristone and acknowledges that the effectiveness of the regimen may be lower if misoprostol is administered less than 24 hours after mifepristone administration.

In addition to your concerns that a woman may take misoprostol too soon after administering mifepristone, you also state that waiting until 24 hours after administering mifepristone does not guarantee success (Petition at 7-8). In support of this concern, you cite a 2015 review by Chen and Creinin. You state that this review found “women taking misoprostol earlier than 48 hours after Mifeprex are more likely to fail the regimen” (Petition at 8). Chen and Creinin included studies in which the intervals between mifepristone and buccal misoprostol were 24 hours or 24-48 hours and stated that “based on the available literature, the overall efficacy of regimens with a 24-hour interval between mifepristone and buccal misoprostol is significantly lower than those with a 24- to 48-hour interval (94.2 percent compared with 96.8 percent).”⁶² The rate differences were statistically significant, but both regimens were more effective than the 92 percent efficacy rate of the original regimen approved in 2000 (administering misoprostol 48 hours after taking mifepristone).

Finally, you also express concern that if misoprostol is self-administered, a woman may swallow it rather than keep the pill between her cheek and gum, and oral administration of

⁵⁹ See https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf.

⁶⁰ 2016 Clinical Review, supra n. 13, at 31 (citing 8 Raymond EG, et al. First-trimester medical abortion with mifepristone 200 mg and misoprostol: a systematic review. *Contraception* 2013;87(1):26-37.)

⁶¹ See https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf.

⁶² See Chen MJ and Creinin MD. Mifepristone with buccal misoprostol for medical abortion. *Obstet Gynecol.* 2015;126(1):12-21; see also 2016 Clinical Review, supra n. 13, at 21.

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misoprostol (i.e., swallowing the pill) following the lower dose of mifepristone in the current regimen is not as effective in ending the pregnancy (Petition at 7). Winikoff et al. specifically studied the use of oral compared to buccal misoprostol 24-36 hours after mifepristone 200 mg with overall success rates of 91.3 percent and 96.2 percent, respectively.⁶³ Both regimens resulted in a greater than 91 percent successful medical abortion. Although the study showed decreased efficacy with oral versus buccal administration in 57-63 days gestational age, there were no statistical differences in other gestational age groupings. Even assuming there is a small proportion of women who are 57-63 days gestational age and use oral administration of misoprostol (rather than buccal as labeled), a small decrease in the reported efficacy in that population would not justify requiring a clinic visit for all women undergoing medical abortion.

Overall, studies support the efficacy of the mifepristone, in a regimen with misoprostol when taken by the patient at home. Therefore, we do not agree that an in-person visit is necessary to manage administration of misoprostol.

iii. Rh-Negative Patients

In the Petition, you state that a follow-up examination is particularly critical for Rh-negative patients and that without that follow-up examination, women will not receive Rhogam after the abortion, increasing their risk of subsequent Rh isoimmunization, which can endanger future pregnancies (Petition at 9). You suggest that a clinic visit after the administration of Mifeprex is important for Rh-negative women to receive Rhogam and that removing the required follow-up visit puts Rh-negative women at risk for isoimmunization. We do not agree.

Rh testing is standard of care in the United States and RhD immunoglobulin (such as Rhogam) should be administered if indicated. Further, administration of RhD immunoglobulin should be given within 72 hours of a sensitizing event (e.g., medical abortion).⁶⁴ However, the facility where the RhD immunoglobulin injection occurs (clinic, hospital or laboratory) is not critical. A shift from medical clinics to hospitals for administration of injections has occurred over the years due to shortages of RhD immunoglobulin and poor reimbursement for RhD immunoglobulin injection from third-party payers.⁶⁵ This has resulted in pregnant women frequently obtaining routine 28-week RhD immunoglobulin injections at hospitals/laboratories with a prescription provided by their healthcare providers. This same process of obtaining RhD immunoglobulin via prescription is available to patients after medical termination of pregnancy and does not require a follow-up clinic visit.

⁶³ Winikoff B, Dzuba, IG, Creinin MD, et al, 2008, Two Distinct Oral Routes of Misoprostol in Mifepristone Medical Abortion, *Obstet Gynecol* 112(6):1303-1310.

⁶⁴ ACOG Practice Bulletin No. 181. Prevention of Rh D Alloimmunization. August 2017.

⁶⁵ See <https://www.mdedge.com/obgyn/article/61083/practice-management/rhogam-injections-payment-levels-vary-among-insurers>.

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In summary, the totality of data on the efficacy and safety of medical abortion at less than 70 days gestation, derived from numerous studies, has characterized the complications and rates of complications for completing medical abortion at home, and the findings show medical abortion at home is both safe and effective without three office visits. We therefore deny your request that the use of mifepristone in a regimen with misoprostol require three office visits by the patient.

c. Contraindications

In the Petition, you assert that critical language contraindicating Mifeprex for patients without access to appropriate emergency medical care was excluded from the 2016 Mifeprex labeling. You cite to a study⁶⁶ and ACOG statements as evidence that medical abortions have greater risks and more need for emergency “operation” than a surgical abortion, particularly for patients in rural areas with limited access to emergency medical care (Petition at 11).

Although inadequate access to medical facilities for appropriate care was removed from the list of contraindications in section 4 of the approved labeling when we approved the S-020 efficacy supplement, the 2016 Mifeprex labeling and the currently approved mifepristone labeling, as well as the Mifepristone REMS Program, continue to include appropriate instructions for providers regarding patient access to appropriate medical care.⁶⁷ For example, the Boxed Warning includes language directing healthcare providers to ensure that the patient knows whom to call and what to do, including potentially going to an emergency room, if the patient experiences serious events associated with the use of mifepristone. The labeling also directs healthcare providers, as part of the dosing regimen, to give the patient the name and phone number of a healthcare provider who will be handling emergencies.⁶⁸ In addition, one of the required qualifications listed in the Prescriber Agreement Form is the “[a]bility to provide surgical intervention in cases of incomplete abortion or severe bleeding, or to have made plans to provide such care through others, and ability to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.”⁶⁹ Therefore, although certain language about access to medical facilities was removed from the approved labeling in 2016, we disagree that critical language about access to appropriate emergency medical care is lacking from the approved labeling.

⁶⁶ See Petition Reference Document No. 17 (Harrison Affidavit: Donna Harrison, M.D., Aff. *Okla. Coalition for Reproductive Justice v. Cline*, Case No. CV-2014-1886 (Feb. 24, 2015), ¶115 (referencing M. Niinimäki et al., Immediate Complications after Medical compared with Surgical Termination of Pregnancy, *Obstet. Gynecol.* 114:795 (Oct. 2009)).

⁶⁷ See Mifeprex labeling, approved 2016.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf. See also current labeling at https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf.

⁶⁸ *Id.*

⁶⁹ Mifepristone REMS Program,

<https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm?event=RemisDetails.page&REMS=390>.

Emphasis added.

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You also cite information in Box 1, Features of Medical and Surgical Abortion (page 3) in the ACOG Practice Bulletin No. 143.⁷⁰ As mentioned above, the ACOG Practice Bulletin No. 143 has been withdrawn and the language you cite is not included in the current Practice Bulletin No. 225.

d. Adverse Event Reporting

In the Petition, you assert that even under the regimen approved in 2000, it was difficult to collect accurate and complete adverse event information for Mifeprex, and that collecting such information is virtually impossible under the regimen approved in 2016 because prescribers only are required to report deaths associated with Mifeprex (Petition at 12). You also assert that FDA cannot adequately assess the safety of the current Mifeprex regimen without comprehensive information on adverse events (Petition at 12). You state that certified prescribers should at a minimum be required to report the following to FDA's MedWatch reporting system and to the sponsor: deaths, hospitalizations, blood transfusions, emergency room visits, failures requiring surgical completion, ongoing pregnancy, or other major complications, including detailed information on these events (Petition at 13).

We acknowledge that there is always a possibility with any drug that some adverse events are not being reported, because reporting to the Agency's MedWatch program by health care professionals and patients is voluntary. We do not agree, however, that the 2016 changes to the prescriber reporting requirements limit our ability to adequately monitor the safety of mifepristone for medical termination of pregnancy. Prior to the 2016 approval of the S-20 efficacy supplement, we assessed approximately 15 years of adverse event reports both from the Applicant and through the MedWatch program and determined that certain ongoing additional reporting requirements under the Mifeprex REMS, such as hospitalization and blood transfusions, were not warranted. This assessment was based on the well-characterized safety profile of Mifeprex, with known risks occurring rarely, along with the essentially unchanged safety profile of Mifeprex during this 15-year period of surveillance. Accordingly, the Prescriber Agreement Form was amended as part of our 2016 approval of the S-20 efficacy supplement to require, with respect to adverse event reporting, only that prescribers report any cases of death to the Applicant.

We also note that the reporting changes to the Prescriber Agreement Form as part of our 2016 approval do not change the adverse event reporting requirements for the Applicants. Like all other holders of approved NDAs and ANDAs, the Applicants are required to report all adverse events, including serious adverse events, to FDA in accordance with the requirements set forth in FDA's regulations (see 21 CFR 314.98, 21 CFR 314.80, and 21 CFR 314.81). FDA also routinely reviews the safety information provided by the Applicants in the Annual Reports. As with all drugs, FDA continues to closely monitor the postmarketing safety data on mifepristone for the medical termination of pregnancy.

⁷⁰ Petition at 11. Medical Management of First-Trimester Abortion. ACOG Practice Bulletin Number 143. March 2014 (Reaffirmed 2016. Replaces Practice Bulletin Number 67, October 2005); Obstet Gynecol. 2014 Mar;123(3):676-692 at 680.

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You state that FDA should provide guidance to emergency healthcare providers and physicians so that they know how to distinguish complications following drug-induced abortion from complications following spontaneous miscarriage (Petition at 13). We disagree that specific guidance is needed at this time. In the past, when appropriate, FDA has worked with the NDA Applicant to issue communications to healthcare providers and emergency department providers concerning certain serious adverse events.⁷¹ Furthermore, the approved Medication Guide advises patients to take the Medication Guide with them if they need to go to the emergency room or seek care from a healthcare provider other than the one who dispensed the medication to them, so the emergency room or healthcare provider understands the patient is having a medical abortion. We have not identified a change in the safety profile of mifepristone that would warrant additional communications to healthcare providers and emergency department providers concerning complications following medical abortion. If we become aware of safety information that merits further communications with emergency department providers or healthcare providers, or that warrants revisions to the approved labeling, we will act as appropriate.

You also assert that many Mifeprex prescribers “violate FDA protocol,” instructing their patients to lie to emergency medical personnel, and that this prevents emergency healthcare providers from appropriately caring for their patients and further decreases the likelihood that adverse events will be reported (Petition at 12). Your only support for this claim is a reference to instructions from the organization Aid Access⁷² to patients that they can tell emergency room staff that they had a miscarriage and do not need to tell medical staff that they had a medical abortion. The Petition does not provide any data or additional information establishing “many Mifeprex prescribers violate FDA protocol, instructing their patients to lie,” or that these providers thereby prevented appropriate care and decreased the number of adverse events reported.

B. REMS

1. Request to Retain Mifeprex REMS

In your Petition, you request that FDA retain the Mifeprex REMS (Petition at 14). We agree that a REMS is necessary to ensure that the benefits of mifepristone in a regimen with misoprostol outweigh the risks. FDA’s determination as to whether a REMS is necessary

⁷¹ See Historical Information on Mifepristone (Marketed as Mifeprex), available at <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111334.htm>. For example, the NDA applicant and FDA agreed that there was a need to issue a Dear Health Care Provider letter in April 2002 and a Dear Emergency Room Director letter in September 2004. The fact that these letters were issued does not imply that the approved mifepristone regimen is unsafe; it is not uncommon for drug sponsors to issue “Dear Health Care Provider” letters, and, as noted in the Mifepristone Q&A document posted on our Web site in April 2002, “[w]hen FDA receives and reviews new information, the agency provides appropriate updates to doctors and their patients so that they have essential information on how to use a drug safely.”

⁷² We note that Aid Access facilitated the sale of unapproved mifepristone and misoprostol to U.S. consumers and that FDA sent Aid Access a warning letter asking it to promptly cease causing the sale of unapproved and misbranded drugs to U.S. consumers. US FDA Warning Letter to Aidaccess.org, dated March 8, 2019. <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/aidaccessorg-575658-03082019>.

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to ensure that the benefits of a drug outweigh its risks is a complex, drug-specific inquiry, reflecting an analysis of multiple, interrelated factors and of how those factors apply in a particular case.⁷³ In conducting this analysis, FDA considers whether (based on premarketing or postmarketing risk assessments) there is a particular risk or risks associated with the use of the drug that, on balance, outweigh its benefits and whether additional interventions beyond FDA-approved labeling are necessary to ensure that the drug's benefits outweigh its risks.⁷⁴

As described in the background section of this response (see section I.A.), FDA determined that interventions in addition to the FDA-approved labeling were necessary to ensure that the benefits of Mifeprex outweighed its risks when the drug was initially approved in 2000, and periodic re-evaluations of the REMS since that time have reached the same conclusion. As further described in the background section of this response (see section I.E.), FDA recently undertook a review of the Mifepristone REMS Program. As explained below, the Mifepristone REMS Program continues to be necessary to ensure the benefits outweigh the risks.

After review of multiple different sources of information, including published literature, safety information submitted to the Agency during the COVID-19 PHE, FAERS reports, the first REMS assessment report for the Mifepristone REMS Program, and information provided by advocacy groups, individuals, and the Plaintiffs in ongoing litigation,⁷⁵ as well as information submitted by the Applicants, we have concluded that the REMS can be modified to reduce the burden on the health care delivery system without compromising patient safety. As explained below, we agree that the healthcare provider certification (ETASU A) and dispensing of mifepristone to patients with evidence or other documentation of safe use conditions (ETASU D) continue to be necessary components of the REMS to ensure the benefits outweigh the risks. However, we have concluded that the Mifepristone REMS Program must be modified to remove the requirement under ETASU C that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals.

Below, we discuss each of these elements of the Mifepristone REMS Program.

a. ETASU A – Prescriber Certification/Qualifications

ETASU A under the Mifepristone REMS Program requires healthcare providers who prescribe mifepristone to be certified. In order to become certified, prescribers must: 1) review the prescribing information for mifepristone and 2) complete the Prescriber Agreement Form. In signing the Prescriber Agreement Form, prescribers agree they meet the qualifications listed below:

⁷³ See FDA Guidance for Industry, *REMS: FDA's Application of Statutory Factors in Determining When a REMS Is Necessary* (Apr. 2019).

⁷⁴ *Id.*

⁷⁵ See *supra* n. 10.

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- Ability to assess the duration of pregnancy accurately
- Ability to diagnose ectopic pregnancies
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or to have made plans to provide such care through others, and ability to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the Prescribing Information of mifepristone (which the provider can access by phone or online).

In addition to meeting these qualifications, as a condition of certification the healthcare provider also agrees to follow the guidelines for use below:

- Review the Patient Agreement Form with the patient and fully explain the risks of the mifepristone treatment regimen. Answer any questions the patient may have prior to receiving mifepristone.
- Sign and obtain the patient's signature on the Patient Agreement Form.
- Provide the patient with a copy of the Patient Agreement Form and the Medication Guide.
- Place the signed Patient Agreement Form in the patient's medical record.
- Record the serial number from each package of mifepristone in each patient's record.
- Report deaths to the Applicant, identifying the patient by a non-identifiable patient reference and the serial number from each package of mifepristone.

Our review of the published literature did not identify any studies comparing healthcare providers who met these qualifications with healthcare providers who did not. In the absence of such studies, there is no evidence to contradict our previous finding that prescribers' ability to accurately date pregnancies, diagnose ectopic pregnancies, and provide surgical intervention either personally or through others, is necessary to mitigate the serious risks associated with the use of mifepristone in a regimen with misoprostol. Therefore, our conclusion continues to be that a healthcare provider who prescribes mifepristone in a regimen with misoprostol should meet the above qualifications. Absent these provider qualifications, we are concerned that serious and potentially fatal complications associated with medical abortion, including missed ectopic pregnancy and heavy bleeding from incomplete abortion, may not be detected or appropriately managed.

Accordingly, we have determined that ETASU A must remain an element of the Mifepristone REMS Program to ensure the benefits outweigh the risks. Maintaining the requirement for prescriber certification ensures that providers meet the necessary qualifications and adhere to the guidelines for use listed above. The burden of prescriber certification has been minimized to the extent possible by requiring prescribers to certify only one-time for each applicant.

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Although we agree with your request to retain the REMS for mifepristone (now the Mifepristone REMS Program) insofar as it pertains to ETASU A, as discussed in section II.A.2.a of this response, we do not agree with your request that the healthcare provider needs to be a licensed physician to meet this requirement.

b. ETASU D – Requirement For The Drug To Be Dispensed With Evidence Or Other Documentation Of Safe-Use Conditions

ETASU D under the Mifepristone REMS Program requires mifepristone to be dispensed with evidence or other documentation of safe-use conditions. To receive mifepristone for medical termination of intrauterine pregnancy through 70 days gestation, the patient must sign a Patient Agreement Form indicating that the patient has received, read, and been provided a copy of the Patient Agreement Form and received counseling from the prescriber regarding the risk of serious complications associated with mifepristone for this indication. The Patient Agreement Form ensures that patients are informed of the risks of serious complications associated with mifepristone for this indication. In a number of approved REMS, Patient Agreement Forms or Patient Enrollment Forms ensure that patients are counseled about the risks of the product and/or informed of appropriate safe use conditions.⁷⁶

As a condition of certification under the Mifepristone REMS Program, healthcare providers must follow the guidelines for use of mifepristone, including reviewing the Patient Agreement Form with the patient, fully explaining the risks of the treatment regimen and answering any questions the patient may have before receiving the medication. With this form, the patient acknowledges that they have received and read the form, and that they have received the counseling regarding when to take mifepristone, the risk of serious complications associated with mifepristone and what to do if they experience adverse events (e.g., fever, heavy bleeding). Both the healthcare provider and patient must sign the document and the patient must receive a copy of the signed form. In addition to the counseling described in the Patient Agreement Form, patients also receive a copy of the Medication Guide for mifepristone. Ultimately, the Patient Agreement Form serves as an important counseling component, and documentation that the safe use conditions of the Mifepristone REMS Program have been satisfied, as the prescriber is required to place the signed Patient Agreement Form in the patient's medical record.

In addition, we conducted an updated review of published literature since 2016 to assess the utility of maintaining the Patient Agreement Form as part of the Mifepristone REMS Program, and these studies do not provide evidence that would support removing ETASU D. For these reasons, we have determined that ETASU D must remain an element of the Mifepristone REMS Program to ensure the benefits outweigh the risks.

⁷⁶ REMS@FDA, <https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm>, Accessed November 15, 2021.

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c. ETASU C – In-Person Dispensing

ETASU C under the Mifepristone REMS Program currently requires mifepristone to be dispensed to patients only in certain healthcare settings, specifically clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber. This creates what we refer to in this response as an in-person dispensing requirement under the REMS; i.e., the patient must be present in person in the clinic, medical office, or hospital when the drug is dispensed. The mifepristone REMS document currently states that mifepristone may not be distributed to or dispensed through retail pharmacies or settings other than a clinic, medical office, or hospital. As explained below, based on a recent review of the REMS, we believe that the Mifepristone REMS Program must be modified to remove the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals, because this requirement is no longer necessary to ensure that the benefits of the drug outweigh the risks. This conclusion is based on our review of information from the Mifepristone REMS Program one-year (1st) REMS⁷⁷ assessment data and postmarketing safety information, and supported by our review of the published literature.

i. Assessment Data

As part of our review of the REMS, we evaluated information included in the 1st REMS assessment report for the Mifepristone REMS Program, which included healthcare provider certification data, program utilization data, and non-compliance data. This 1st REMS assessment report covers a reporting period between April 11, 2019 through February 29, 2020. During this reporting period, a small number of non-compliance events were reported.

As described in section I.C. of this response, during the timeframe from January 27, 2020 through September 30, 2021, there were periods when the in-person dispensing requirement was not enforced. To better understand whether there was any impact on safety or non-compliance during the periods when the in-person dispensing requirement was not enforced, we requested additional information from the Applicants to provide for more comprehensive assessment of the REMS for the time period from January 27, 2020 (the effective date of the COVID-19 PHE) to September 30, 2021. We requested the Applicants provide a summary and analysis of any program deviation or non-compliance events from the REMS requirements and any adverse events that occurred during this time period that had not already been submitted to FDA. The NDA and the ANDA Applicants reported a total of eight cases reporting adverse events between January 27, 2020 and September 30, 2021. These eight cases were also identified in the FAERS database and are described below.

The number of adverse events reported to FDA during the COVID-19 PHE with mifepristone use for medical termination of pregnancy is small, and the data provide no

⁷⁷ This REMS assessment report was the first submitted following the approval of the single, shared system REMS for mifepristone.

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indication that any program deviation or noncompliance with the Mifepristone REMS Program contributed to these reported adverse events.

ii. FAERS/Postmarketing Safety Data

FDA routinely monitors postmarketing safety data for approved drugs through adverse events reported to our FAERS database,⁷⁸ through our review of published medical literature, and when appropriate, by requesting applicants submit summarized postmarketing data. For our recent review of the REMS, we searched our FAERS database, reviewed the published medical literature for postmarketing adverse event reports for mifepristone for medical termination of pregnancy, and requested that the Applicants submit a summary and analysis of certain adverse events. Our review of this postmarketing data indicates there have not been any new safety concerns with the use of mifepristone for medical termination of pregnancy through 70 days gestation, including during the time when in-person dispensing was not enforced.

In order to evaluate the periods when in-person dispensing was and was not enforced, we conducted a search of the FAERS database and the published medical literature to identify U.S. postmarketing adverse events that reportedly occurred from January 27, 2020 through September 30, 2021 with mifepristone use for medical termination of pregnancy. The data for this time period were then further divided into the date ranges when in-person dispensing was enforced per the REMS (January 27, 2020 - July 12, 2020 and January 13, 2021 - April 12, 2021) versus when in-person dispensing was not enforced: July 13, 2020 - January 12, 2021 (in-person dispensing enforcement was temporarily enjoined) and April 13, 2021 - September 30, 2021 (enforcement discretion for in-person dispensing because of the COVID-19 PHE).

Based on the above search, a total of eight cases were identified in FAERS and no additional case reports were identified in the medical literature. Two of the eight cases reported adverse events that occurred when in-person dispensing was being enforced (i.e., January 27, 2020-July 12, 2020 and January 13, 2021-April 12, 2021). These two cases reported the occurrence of uterine/vaginal bleeding (case 1) and uterine/vaginal bleeding and sepsis (case 2). Of note, uterine/vaginal bleeding and sepsis are labeled adverse events. Five of the eight cases reported adverse events that occurred when in-person dispensing was not enforced (i.e., July 13, 2020-January 12, 2021 and April 13, 2021-September 30, 2021); however, the narratives provided in the FAERS reports for three of the five cases explicitly stated that mifepristone was dispensed in-person. These five cases reported the occurrence of ongoing pregnancy (case 3), drug intoxication and death approximately 5 months after ingestion of mifepristone (case 4), death [cause of death is currently unknown] (case 5), sepsis and death (case 6), and pulmonary embolism (case 7). Of note, ongoing pregnancy and sepsis, including the possibility of fatal septic shock, are labeled adverse events. The remaining case reported the occurrence of oral pain/soreness (case 8) in July

⁷⁸ FAERS is a database that contains adverse event reports, medication error reports and product quality complaints resulting in adverse events that were submitted to FDA. The database is designed to support FDA's post-marketing safety surveillance program for drug and therapeutic biologic products.

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2021, but did not provide sufficient information to determine the exact date of the adverse event.

As discussed in section II.A.2.d., the Applicants report adverse events, including serious adverse events, to FDA in accordance with applicable regulations.⁷⁹ To enable additional review of adverse events, Applicants were requested to provide a summary and analysis for adverse events reported with incomplete medical abortion requiring surgical intervention to complete abortion, blood transfusion following heavy bleeding or hemorrhage, ectopic pregnancies, sepsis, infection without sepsis, hospitalization related to medical abortion, and emergency department/urgent care encounter related to medical abortion. The Applicant for Mifeprex provided the requested summary of postmarketing safety information from March 29, 2016, when S-020 was approved, through September 30, 2021. The Applicant for the generic provided the requested summary of postmarketing safety information from April 11, 2019 (date of initial approval) through September 30, 2021. The information provided by the Applicants included the same cases identified in FAERS, as discussed above.

We analyzed the FAERS data referenced above to determine if there was a difference in adverse events when in-person dispensing was and was not enforced. Based on FDA's review of this data, we concluded that there does not appear to be a difference in adverse events when in-person dispensing was and was not enforced and that mifepristone may be safely used without in-person dispensing. FDA's review of the summary and analysis data submitted by the Applicants (which, as noted above, included the same cases identified from FAERS) did not change this conclusion.

iii. Published Literature

As noted above, we also conducted an extensive review of the published literature since March 29, 2016 (the date the S-020 efficacy supplement for Mifeprex was approved) through September 30, 2021.⁸⁰ Published studies have described alternatives in location and method for dispensing mifepristone by a certified prescriber (or equivalent healthcare provider in countries other than the United States). Some studies have examined replacing in-person dispensing in certain healthcare settings with dispensing at retail pharmacies⁸¹

⁷⁹ See 21 CFR 314.98, 21 CFR 314.80, and 21 CFR 314.81.

⁸⁰ In support of your request that we retain the REMS and continue limiting the dispensing of Mifeprex to patients in clinics, medical offices, and hospitals by or under the supervision of a certified prescriber, you reference two studies that you assert do not comply with the REMS (Petition at 19-22). Outcomes from both of the studies you reference have been reported in the published literature and are addressed in the discussion that follows. We note that as a general matter, a clinical investigation of an approved drug that is subject to a REMS can take place in healthcare settings outside those provided for in the REMS. When an approved drug that is subject to a REMS is studied in a clinical trial, the REMS does not apply to the use of the drug in that clinical trial. However, FDA reviews the protocol to ensure that it will be conducted in a manner that adequately addresses the risks that the REMS is intended to mitigate, such that the trial participants will not be exposed to an unreasonable and significant risk of illness or injury. See 21 CFR 312.42(b)(1)(i) and (b)(2)(i).

⁸¹ Grossman D, Baba CF, Kaller S, et al. Medication Abortion With Pharmacist Dispensing of Mifepristone. *Obstet Gynecol* 2021;137:613–22; Rocca CH, Puri M, et al. Effectiveness and safety of early medication

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and dispensing mifepristone from pharmacies by mail.⁸² Other studies have evaluated two modes of dispensing by prescribers: (1) prescribers mailing the medications to patients,⁸³ and (2) prescribers using couriered delivery of medications.⁸⁴ Different studies have evaluated dispensing mifepristone by mail by an entity described as “a partner organization.”⁸⁵

We note that the ability to generalize the results of these studies to the United States population is hampered by differences between the studies with regard to pre-abortion care (e.g., telemedicine versus in-person). In addition, the usefulness of the studies is limited in some instances by small sample sizes and lack of follow-up information on outcomes with regard to both safety and efficacy. There are also factors which complicate the analysis of the dispensing element alone. Some of these factors are: (1) only a few studies have evaluated alternatives for in-person dispensing of mifepristone in isolation (for example, most studies on mail dispensing of mifepristone also include telemedicine consultation); and (2) because most serious adverse events with medical abortion are infrequent, further evaluation of changes in dispensing would require studies with larger numbers of participants. We did not find any large clinical studies that were designed to collect safety outcomes in healthcare systems similar to the United States. Despite the limitations of the studies we reviewed, we have concluded that overall the outcomes of these studies are not inconsistent with our conclusion that, based on the 1st year REMS assessment report and postmarketing safety data, mifepristone will remain safe and efficacy will be maintained if the in-person dispensing requirement is removed from the Mifepristone REMS Program.

abortion provided in pharmacies by auxiliary nurse-midwives: A non-inferiority study in Nepal. *PLoS ONE* 13(1): e0191174. <https://doi.org/10.1371/journal.pone.0191174>; Wiebe ER, Campbell M, et al. Comparing telemedicine to in-clinic medication abortions induced with mifepristone and misoprostol. *Contracept X*. 2020; 2: 100023.

⁸² Grossman D, Raifman S, Morris N, et.al. Mail-order pharmacy dispensing of mifepristone for medication abortion after in-person clinical assessment. *Contraception* 2021, ISSN 0010-7824, <https://doi.org/10.1016/j.contraception.2021.09.008>, Available online 20 September 2021; Upadhyay UD, Koenig LR, Meckstroth KR. Safety and Efficacy of Telehealth Medication Abortion in the US During the COVID-19 Pandemic. *JAMA Network Open*. 2021;4(8):e2122320, doi:10.1001/jamanetworkopen.2021.22320; Hyland P, Raymond EG, Chong E. A direct-to-patient telemedicine abortion service in Australia: Retrospective analysis of the first 18 months. *Aust N Z J Obstet Gynaecol* 2018;58: 335-340.

⁸³ See Anger HA, Raymond EG, et al. Clinical and service delivery implications of omitting ultrasound before medication abortion provided via direct-to-patient telemedicine and mail. *Contraception* 2021 Jul 28;S0010-7824(21)00342-5. doi: 10.1016/j.contraception.2021.07.108. Published online. Raymond E, Chong E, et al. TelAbortion: evaluation of a direct to patient telemedicine abortion service in the United States. *Contraception* 2019; 100:173-177. See also Chong et al., *infra* n. 103 Kerestes et al., *infra* n. 105, and Aiken et al., *infra* n. 106.

⁸⁴ Reynolds-Wright JJ, et al. *BMJ Sex Reprod Health* 2021;0:1–6. doi:10.1136/bmj.srh-2020-200976.

⁸⁵ Endler M, Beets L, Gemzell Danielsson K, Gomperts R. Safety and acceptability of medical abortion through telemedicine after 9 weeks of gestation: a population-based cohort study. *BJOG* 2019;126:609-618. Norton H, Ilozumba O, Wilkinson J, Gemzell Danielsson K, Gomperts R. 10-year evaluation of the use of medical abortion through telemedicine: a retrospective cohort study. *BJOG* 2021; <https://doi.org/10.1111/1471-0528.16765>; Aiken ARA, Digol I, Trussell J, Gomperts R. Self-reported outcomes and adverse events after medical abortion through online telemedicine: population based study in the Republic of Ireland and Northern Ireland. *BMJ* 2017;357:j2011 <http://dx.doi.org/10.1136/bmj.j2011>.

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Below is a summary of our review of the literature, organized by the methods of dispensing mifepristone that were studied.

(a) Retail pharmacy dispensing

Three studies reported medical abortion outcomes for retail pharmacy dispensing of mifepristone after clinical evaluation (Grossman,⁸⁶ Rocca,⁸⁷ Wiebe⁸⁸). Grossman conducted a US-based study in which mifepristone and misoprostol were dispensed from a pharmacy partnered with the clinic. Complete abortion without additional procedures occurred in 93.5 percent of participants with known outcomes. The reported proportion of complete abortion is within the range described in the approved mifepristone labeling. No participants experienced a serious adverse event, were hospitalized or required transfusion. Three participants had emergency department (ED) visits with treatment (intravenous hydration, pain medication, pelvic infection after uterine aspiration for incomplete abortion). The study safety and efficacy outcomes are consistent with labeled outcome frequencies. The study has limited generalizability because it was conducted in two US states and involved partnered pharmacies, some of which were in the same building as the clinic. Additionally, all participating pharmacies in this study were required to have a pharmacist on duty during clinic hours who had been trained in the study protocol and was willing to dispense mifepristone. The study conditions may not be generalizable to United States retail pharmacies; there is insufficient information to assess this.

Rocca⁸⁹ conducted an observational study evaluating participants who obtained medical abortions in Nepal by comparing the provision of medical abortion service by newly trained nurse midwives in pharmacies to medical abortion provided in government-certified clinics. The authors reported that, with respect to complete abortion (greater than 97 percent) and complications (no hospitalizations or transfusions), evaluation and dispensing in pharmacy was non-inferior to in-clinic evaluation and dispensing.

Wiebe,⁹⁰ in a retrospective, chart review study conducted in Canada, compared abortion outcomes of women who underwent medical abortion with telemedicine consult, and either received medications by courier or picked them up at a local pharmacy, with outcomes of a matched control cohort of women who received the medications at a pharmacy after an in-clinic visit. The groups had similar documented complete medical abortion outcomes (equal to or greater than 95 percent participants with known outcomes). The telemedicine group had one case of hemorrhage (0.5 percent) and one case of infection requiring antibiotics (0.5 percent) compared with no cases of hemorrhage or infection requiring antibiotics in the in-clinic cohort. The telemedicine group had more ED visits (3.3 percent compared to 1.5 percent in-clinic cohort). Both models of dispensing mifepristone resulted in efficacy and safety outcomes within labeled frequency.

⁸⁶ Grossman et al., supra n. 81.

⁸⁷ Rocca et al., supra n. 81.

⁸⁸ Wiebe et al., supra n. 81.

⁸⁹ Rocca et al., supra n. 81.

⁹⁰ Wiebe et al., supra n. 81.

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None of the three studies allow a determination regarding differences in safety between in-person dispensing by a certified prescriber in a health care setting and dispensing through a retail pharmacy, due to limitations on the generalizability of the results of the studies to the current retail pharmacy environment in the United States. The outcome findings from the one United States study (Grossman)⁹¹, in which the pharmacies were partnered with prescribers, are unlikely to be broadly generalizable to the current retail pharmacy environment and do not reflect typical prescription medication availability with use of retail pharmacy dispensing. For the retail pharmacy dispensing study in Canada (Wiebe),⁹² timely provision of medication from the retail pharmacy was accomplished by either courier to the woman or faxed prescription to the woman's pharmacy. It is unknown whether conditions that would allow timely access to medications for medical abortion would occur in retail pharmacies throughout the United States, suggesting the findings from that study may not be broadly generalizable. The third study (Rocca)⁹³ evaluated medical abortion provided in Nepali pharmacies and essentially moved the abortion provider and clinical examination into the pharmacy, a scenario that is not, at this time, applicable to the United States retail setting.

(b) Mail order pharmacy

Three studies evaluated mail order pharmacy dispensing (Grossman,⁹⁴ Upadhyay,⁹⁵ Hyland⁹⁶). Grossman published an interim analysis of an ongoing prospective cohort study evaluating medical abortion with mifepristone and misoprostol dispensed by mail-order pharmacy after in-person clinical assessment. Complete abortion without additional procedures occurred in 96.9 percent of participants with known outcomes. Two (0.9 percent) participants experienced serious adverse events; one received a blood transfusion and one was hospitalized overnight. Nine (4 percent) participants attended 10 ED visits. In this interim analysis, the outcomes are consistent with labeled frequencies.

Upadhyay⁹⁷ reports findings from a retrospective cohort study of women undergoing medical abortion in the United States without a consultation or visit. Eligibility was assessed based on a participant-completed online form collecting pregnancy and medical history. Participants who were considered eligible received medication delivered by a mail-order pharmacy. Abortion outcome was determined by either an assessment on day 3 or a 4-week pregnancy test. The investigators reported a complete abortion rate without additional procedures of 95 percent for participants with known outcomes and stated that no participants had any major adverse events. The proportion of abortion outcomes assessed at 3 days versus 4 weeks is not reported. Regardless, determining outcomes at 3 days is insufficient to determine outcome rates or safety findings because a 3-day follow-up period is too short. As recommended in Section 2.3 of the approved labeling, follow-up at

⁹¹ Grossman et al., supra n. 81.

⁹² Wiebe et al., supra n. 81.

⁹³ Rocca et al., supra n. 81.

⁹⁴ Grossman et al., supra n. 82.

⁹⁵ Upadhyay et al., supra n. 82.

⁹⁶ Hyland et al., supra n. 82.

⁹⁷ Upadhyay et al., supra n. 82.

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7-14 days after administration of mifepristone is more appropriate to evaluate safety and efficacy. This study used a model with numerous deviations from standard provision of medical abortion in the United States, such as no synchronous interaction with the prescriber during informed consent or prior to prescribing medication and no confirmation of self-reported medical, surgical, and menstrual history. These deviations, limited follow-up information, and small sample size limit the usefulness of this study.

Hyland⁹⁸ describes findings from a cohort study in Australia evaluating medical abortion outcomes utilizing telemedicine and a central mail order pharmacy. Complete abortions without additional procedures occurred in 96 percent of participants with documented outcomes and is consistent with labeled efficacy. Of the participants included in the analysis, 95 percent had no face-to-face clinical encounters after medications were mailed while 3 percent were admitted to the hospital and 2 percent had an outpatient encounter. One participant who was hospitalized and underwent a surgical uterine evacuation received a transfusion. Not included in the findings are 7 hospitalizations occurring in 7 participants who did not have “full follow up.” The authors do not report any other adverse events and conclude use of the telemedicine medical abortion service is safe. However, the reasons for hospitalization are not discussed by the authors; therefore, it is unknown why the patients were hospitalized. Although the reported frequency of hospitalizations (3 percent) is higher than the less than 1 percent in the FDA-approved mifepristone labeling, conclusions on the safety findings cannot be made in the absence of information about the reasons for hospitalization. Other limitations of this study include incomplete information about outcomes with face-to-face encounters.

Overall, the three studies evaluating mail order pharmacy dispensing suggest that efficacy of medical abortion is maintained with mail order pharmacy dispensing. With respect to safety, in the Grossman study⁹⁹ the interim analysis, although small, does not raise serious safety concerns. Safety findings from the Hyland¹⁰⁰ study are difficult to interpret. Although only one transfusion is reported and the authors state the findings demonstrate safety, a higher hospitalization rate and lack of information on the reasons for hospitalization preclude reaching any conclusions about the safety findings. Lastly, the Upadhyay¹⁰¹ study had no reported adverse events, but the findings are less useful because of the limited follow-up, and because medical abortions were provided using a model with numerous deviations from standard provision of medical abortion in the United States.

(c) Clinic dispensing by mail

A total of five studies evaluated clinic dispensing by mail. Gynuity Health Projects conducted a prospective cohort study (the “TelAbortion” study) evaluating use of telemedicine for remote visits and mifepristone being dispensed from clinics via overnight or regular tracked mail. Three publications reviewed have reported outcomes for the Gynuity population exclusively: Raymond (outcomes from May 2016 to December

⁹⁸ Hyland et al., supra n. 82.

⁹⁹ Grossman et al., supra n. 82.

¹⁰⁰ Upadhyay et al., supra n. 82.

¹⁰¹ Hyland et al., supra n. 82.

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2018),¹⁰² Chong (outcomes from May 2016 to September 2020)¹⁰³ and Anger (outcomes from March 2020 to September 2020).¹⁰⁴ A fourth study, Kerestes,¹⁰⁵ reports outcomes of medical abortion at the University of Hawai'i from April 2020 to November 2020 and a fifth study, Aiken (2021)¹⁰⁶ reports outcomes of medical abortion up to 70 days gestational age in the United Kingdom before and during the COVID-19 PHE in a retrospective cohort study.

In Raymond,¹⁰⁷ complete abortion without additional procedures occurred in 93 percent of participants with known outcomes. There were two hospitalizations (one participant received a transfusion for severe anemia despite having had a complete abortion) and 7 percent of participants had clinical encounters in ED/urgent care centers. The reported outcomes are similar to outcomes described in approved labeling except the combined ED/urgent care center encounters (7 percent) exceeded the ED visits in approved labeling (2.9-4.6 percent).¹⁰⁸ Of note, the authors state that half of the ED/urgent care visits did not entail any medical treatment. In Chong,¹⁰⁹ approximately 50 percent of the medical abortions occurred during the period of the COVID-19 PHE. Complete abortion without an additional procedure occurred in 95 percent of those with known outcomes. Transfusions were 0.4 percent and hospitalizations were 0.7 percent; 6 percent of participants had unplanned clinical encounters in ED/urgent care. Surgical interventions were required in 4.1 percent to complete abortion. The reported outcomes in Chong (which updated the findings described in Raymond) are similar to outcomes described in approved labeling except that (as with the Raymond study it updated) the combined ED/urgent care center encounters (6 percent) exceeded the ED visits in approved labeling (2.9-4.6 percent).

Anger,¹¹⁰ which compared outcomes among participants enrolled in the Gynuity study who did ("test medical abortion cohort") versus did not ("no-test medical abortion cohort")¹¹¹

¹⁰² Raymond et al., *supra* n. 83.

¹⁰³ Chong E, Shochet T, et al. Expansion of a direct-to-patient telemedicine abortion service in the United States and experience during the COVID-19 pandemic. *Contraception* 2021;104:43-48.

¹⁰⁴ Anger et al., *supra* n. 83.

¹⁰⁵ Kerestes C, Murayama S, et al. Provision of medication abortion in Hawai'i during COVID-19: Practical experience with multiple care delivery models. *Contraception* 2021 Jul;104(1):49-53. doi:10.1016/j.contraception.2021.03.025. Epub 2021 Mar 28.

¹⁰⁶ Aiken ARA, Lohr PA, et al. Effectiveness, safety and acceptability of no-test medical abortion (termination of pregnancy) provided via telemedicine: a national cohort study. *BJOG* 2021;128:1464-1474.

¹⁰⁷ Raymond, *supra* n. 83.

¹⁰⁸ The authors reported the combined frequency of emergency department/urgent care visits, whereas the approved labeling includes the frequency for emergency department (emergency room) visits. Therefore it is unknown whether the frequency of emergency department visits in the trial, as distinct from the combined frequency of emergency department/urgent care visits, is comparable to the frequency of emergency department visits reflected in approved labeling.

¹⁰⁹ Chong et al., *supra* n. 103.

¹¹⁰ Anger et al., *supra* n. 83.

¹¹¹ "No-test medication abortion" refers to medical abortion provided without a pretreatment ultrasound, pelvic examination or laboratory tests when, in the judgment of the provider, doing so is medically appropriate (appropriateness based on history and symptoms); "no-test medication abortion" does include post-abortion follow up. A sample protocol is described by Raymond et al." (Raymond EG, Grossman D, Mark A, et.al. Commentary: No-test medication abortion: A sample protocol for increasing access during a pandemic and beyond. *Contraception* 2020;101:361-366)

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have confirmation of gestational age/intrauterine location with an examination or ultrasound, found that those without an examination or ultrasound prior to medical abortion were more likely to require procedural interventions and had more unplanned clinical encounters.¹¹² There were no reported ectopic pregnancies in either group. The number of ED/urgent care visits and the proportion of unplanned clinical encounters that led to medical treatment were not reported. In the “test” group, complete medical abortion was confirmed in 98 percent of participants with known outcomes; one participant was “hospitalized and/or blood transfusion” and 8 percent had an unplanned clinic encounter (participant sought in-person medical care related to abortion and the visit was not planned prior to abortion). In the “no-test” group, complete medical abortion was confirmed in 94 percent of participants with known outcomes; two participants were “hospitalized and/or blood transfusion” and 12.5 percent had an unplanned clinical encounter.

Kerestes¹¹³ included three different delivery models: traditional in-person visits, telemedicine consultation with in-person pick-up of medications, and telemedicine consultation with delivery of medications by mail (most of the latter were enrolled through Gynuity’s TelAbortion study). Among participants with follow-up data, the rates of successful medical abortion without surgery were consistent with outcomes in approved labeling. Blood transfusion was given to two participants (both in the telemedicine plus in-person pickup group). Although ED visits occurred the most frequently in the telemedicine plus mail group (four participants or 5.8 percent) and the least in the in-person group (two participants or 2.1 percent), the study reported no increases in other serious adverse events. Aiken (2021)¹¹⁴ reported outcomes before and during the pandemic in a retrospective cohort study in the United Kingdom. The study compared the two cohorts: one before the pandemic with in-person visits and dispensing (traditional model) and one during the pandemic with either an in-person visit and in-person dispensing or a telemedicine visit and dispensing by mail or picked up from the clinic (hybrid model). Complete abortion occurred in greater than 98 percent in both cohorts; the rate was slightly higher in the telemedicine group than in the in-person group. There were no significant differences in the rates of reported serious adverse events. The investigators’ analysis determined that the efficacy and safety were comparable between both cohorts and concluded the hybrid model for medical abortion is effective and safe.

Taken together, data from the three Gynuity study reports (Raymond, Chong, and Anger), Kerestes, and Aiken (2021) support that efficacy of medical abortion was maintained when mifepristone was dispensed by mail from the clinic. Study reports of Raymond, Chong, and Kerestes all suggest there may be an increase in ED/urgent care visits with telemedicine visits and dispensing by mail from the clinic, but without increases in other serious adverse events. Anger’s comparative analysis suggests a pre-abortion examination may decrease the occurrence of procedural intervention and decrease the number of unplanned visits for postabortion care. The Aiken (2021) study appears to be of sufficient

¹¹² We note that the two cohorts were not randomized in the Anger study; they had different baseline characteristics. Consequently, findings based on the comparisons between the two cohorts should be interpreted carefully.

¹¹³ Kerestes et al., *supra* n. 105.

¹¹⁴ Aiken et al., *supra* n. 106.

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sample size to determine whether safety outcomes with mail dispensing differ from in-person dispensing; however, significant limitations include that the analysis was based on deidentified information and the investigators were unable to verify the outcomes extracted. Further, the study's design did not capture all serious safety outcomes, thus limiting the certainty of the findings.

Notwithstanding the limitations discussed above, these studies overall support that dispensing by mail from the clinic is safe and effective. Although the literature suggests there may be more frequent ED/urgent care visits related to the use of mifepristone when dispensed by mail from the clinic, there are no apparent increases in other serious adverse events related to mifepristone use.

(d) Clinic dispensing by courier

Reynolds-Wright¹¹⁵ reported findings from a prospective cohort study of participants at less than 12 weeks gestational age in Scotland undergoing medical abortion at home that provided mifepristone for pick up at the service or by couriered delivery to woman's home. The outcomes from this study in Scotland are consistent with the outcomes in the approved mifepristone labeling. However, the number of couriered deliveries was not reported. Thus this study does not provide abortion outcomes separately for couriered delivery of mifepristone and misoprostol. The study shares the same limitations as the Aiken (2021) study; the study's design did not capture all serious safety outcomes, thus limiting the certainty of the findings.

(e) Partner organization dispensing by mail

Women on Web (WoW), an internet group, connects patients and providers outside of the US and provides medical abortion globally, dispensing mifepristone through "a partner organization" by mail. WoW uses a model with numerous deviations from the standard provision of medical abortion in the United States. For example, this model has no synchronous interaction with the prescriber during informed consent or prior to prescribing medication and no confirmation of self-reported medical, surgical, and menstrual history or confirmed pregnancy testing. Three studies (Endler, Norten, and Aiken (2017))¹¹⁶ reported outcomes based on dispensing through this model. Endler and Norten reported outcomes from WoW cohorts but do not provide relevant information on mifepristone dispensing by mail because neither provide meaningful outcomes data for consideration. Although Aiken (2017) is a large cohort study, the outcomes are self-reported and an unusually high rate of outcomes are unaccounted for; these limitations result in the data being insufficient to determine the safety of dispensing mifepristone by mail through a partner organization.

In sum, there are insufficient data from the literature we have reviewed to determine the safety and efficacy of dispensing from a retail pharmacy, by courier, or by a partner organization. With respect to dispensing mifepristone by mail, our review of the literature indicates that dispensing mifepristone by mail from the clinic or from a mail order

¹¹⁵ Reynolds-Wright JJ, et al. BMJ Sex Reprod Health 2021;0:1–6. doi:10.1136/bmjshr-2020-200976.

¹¹⁶ Endler et al., Norten et al., and Aiken et al., supra n. 85.

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pharmacy does not appear to jeopardize the efficacy of mifepristone for medical abortion. While the studies we reviewed are not adequate on their own to establish the safety of the model of dispensing mifepristone by mail, the safety and efficacy outcomes reported in these studies remain within the ranges labeled for the approved mifepristone products. Although the literature suggests there may be more frequent ED/urgent care visits related to the use of mifepristone when dispensed by mail from the clinic, there are no apparent increases in other significant adverse events related to mifepristone use.

Based on the REMS assessment data, FAERS data from the time period when the in-person dispensing requirement was not being enforced, and our review of the literature, we conclude that mifepristone will remain safe and effective if the in-person dispensing requirement is removed, provided all the other requirements of the REMS are met and pharmacy certification is added. Removing the in-person dispensing requirement will render the REMS less burdensome to healthcare providers and patients, and provided all other requirements of the REMS are met, including the additional requirement for pharmacy certification, the REMS will continue to ensure that the benefits of mifepristone for medical abortion outweigh the risks. Therefore, to reduce the burden imposed by the Mifepristone REMS Program, the REMS must be modified to remove the in-person dispensing requirement, which would allow, for example, dispensing of mifepristone by mail via certified prescribers or pharmacies, in addition to in-person dispensing in clinics, medical offices and hospitals as currently outlined in ETASU C.

In your Petition, you state that “[e]liminating or relaxing the REMS to facilitate Internet or telephone prescriptions would be dangerous to women and adolescent girls” and that “health care providers prescribing abortion-inducing drugs over the Internet or phone or before a patient is even pregnant cannot adequately evaluate patients for contraindications to the drugs” (Petition at 18-19).

We do not agree that eliminating the REMS requirement for the dispensing of Mifeprex in certain healthcare settings will be dangerous to patients, nor do we agree that doing so will affect the ability of healthcare providers to evaluate women for contraindications to mifepristone in a regimen with misoprostol for medical termination of intrauterine pregnancy through 70 days gestation. There are many factors that contribute to patient safety, including evaluation of a patient, informed consent, development of a follow-up plan, and provision of a contact for emergency care. All of these can occur in many types of healthcare settings. The evaluation of patients for contraindications to medical abortion does not necessarily require direct physical contact with the certified prescriber.

You also assert that telemedicine abortion absolves abortion providers of responsibility for the well-being of their patients (Petition at 19). We do not agree. Healthcare providers who prescribe mifepristone are responsible for the well-being of their patients regardless of mode of evaluation or dispensing of medication. The Agency agrees with the American Medical Association that a healthcare provider-patient relationship is entered when the “physician serves a patient’s medical needs;”¹¹⁷ in the context of medical abortion, this

¹¹⁷ See www.ama-assn.org/delivering-care/ethics/patient-physician-relationships.

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healthcare provider-patient relationship continues until resolution of the pregnancy or transfer of care to another healthcare provider.¹¹⁸

We also note that patients who are not pregnant at the time of evaluation would not be appropriate candidates for being prescribed mifepristone for medical termination of pregnancy because they do not fulfill the approved indication of having an intrauterine pregnancy of up to 70 days gestation.

2. Other Safety Issues and Additional Studies

In support of your request that we retain the Mifeprex REMS, you cite the Council for International Organizations of Medical Sciences' (CIOMS) definition of "rare" to assert that because "about 1 out of 100 women" using Mifeprex and misoprostol require surgery, serious complications are common, not rare (Petition at 15-16).¹¹⁹ Although we agree that certain elements of the Mifepristone REMS Program are necessary to assure the safe use of mifepristone, we do not agree with your assertion.

In the Petition, you state that the Medication Guide improperly downplays the risks of the use of Mifeprex in a regimen with misoprostol and you cite the Medication Guide as stating "'rarely, serious and potentially life-threatening bleeding, infections, and other problems can occur following . . . medical abortion.' Specifically, 'in about 1 out of 100 women [administered Mifeprex and misoprostol] bleeding can be so heavy that it requires a surgical procedure.'" (Petition at 15). Using these two separate statements in the Medication Guide, you argue that the CIOMS's definition of rare ("1 out of 1000") means that if 1 out of 100 women using Mifeprex in a regimen with misoprostol require surgery, serious complications are common, not rare. (Petition at 16). However, your reference to the two sentences in the Medication Guide conflates two different clinical scenarios: (1) the adverse event of serious and potentially life-threatening bleeding, and (2) treatment failure.

The first sentence you reference states: "Although cramping and bleeding are an expected part of ending a pregnancy, rarely, serious and potentially life-threatening bleeding, infections, or other problems can occur following a miscarriage, surgical abortion, medical abortion, or childbirth." This statement refers to life-threatening adverse events that can occur during termination regardless of gestational age or during miscarriage or childbirth regardless of the mode of delivery (e.g., vaginal delivery or cesarean section). At the time of our review of the clinical studies submitted to support the S-020 efficacy supplement, the reported rate of death in the studies reviewed, based on one death, was 0.007 percent (very rare under the CIOMS definition).¹²⁰ The rate of infections requiring hospitalization or

¹¹⁸ See <https://www.ama-assn.org/delivering-care/ethics/ethical-practice-telemedicine>.

¹¹⁹ Council for International Organizations of Medical Sciences. Guidelines for Preparing Core Clinical Safety Information on Drugs Second Edition. 1999. <https://cioms.ch/wp-content/uploads/2018/03/Guidelines-for-Preparing-Core-Clinical-Safety-Info-Drugs-Report-of-CIOMS-Working-Group-III-and-V.pdf>. Accessed December 13, 2021 (CIOMS).

¹²⁰ Id. at 36 (defining the "very rare" standard category of frequency as less than 0.01 percent).

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intravenous antibiotics was less than 0.1 percent (rare under the CIOMS definition),¹²¹ and rates of transfusion were 0.03-0.7 percent (rare to uncommon under the CIOMS definition).¹²² Therefore, “rarely” accurately refers to the frequency of the adverse events referenced in this statement.

The second sentence you reference from the Medication Guide states: “In about 1 out of 100 women, bleeding can be so heavy that it requires a surgical procedure (surgical aspiration or D&C).” This statement refers to the rate of surgical procedures for bleeding following treatment with mifepristone. Heavy bleeding or hemorrhage after medical abortion is a small subset of bleeding and can require a surgical procedure due to ongoing pregnancy or incomplete expulsion; these are considered failed treatment rather than adverse events and are not characterized using the CIOMS definitions. Even if heavy, bleeding after medical abortion may not be considered a serious adverse event unless clinically diagnosed as hemorrhage or requiring a transfusion. Furthermore, in the vast majority of medical abortions, surgical intervention is not necessary.

You also cite a 2009 study and a 2018 study to assert that medical abortions carry greater risks than surgical abortions (Petition at 16). The 2009 Niinimäki, et al.¹²³ study reported overall incidences of immediate adverse events (up to 42 days) in medical and surgical abortions performed in women undergoing induced abortion from 2000-2006 based on data from the Finnish national registries. We agree that the overall incidence of adverse events for medical abortion was fourfold higher when compared with surgical abortion (20.0 percent versus 5.6 percent). Specifically, the incidence of hemorrhage, incomplete abortion, and surgical (re)evacuation were higher for medical abortion. However, the authors specifically noted that because medical abortion is associated with longer uterine bleeding, the high rate of events, which were pulled from a national registry reflecting both inpatient and outpatient visits, is not surprising. They opined that uterine bleeding requiring surgical evacuation probably better reflects the severity of bleeding after termination of pregnancy; the incidence of such bleeding was relatively low, although it was more common with medical abortion. In addition, the authors acknowledged there are inherent weaknesses in registry-based studies; there is variable reliability both of diagnoses and of severity of diagnoses. Nevertheless, the authors concluded that both methods are generally safe and recommended discussing the adverse event profiles of different methods when counseling women seeking pregnancy termination.

We note that Ireland, et al.¹²⁴ reported findings from a more recent retrospective cohort study of 30,146 United States women undergoing pregnancy termination before 64 days of gestation from November 2010 to August 2013. Efficacy of pregnancy termination was 99.6 percent and 99.8 percent for medical and surgical abortion, respectively.

¹²¹ Id. at 36 (defining the “rare” standard category of frequency as greater than or equal to 0.01 percent and less than 0.1 percent).

¹²² Id. at 36 (defining the “uncommon” standard category of frequency as greater than or equal to 0.1 percent and less than 1 percent); see also 2016 Clinical Review, *supra* n. 13, at 47 and 51.

¹²³ Niinimäki M, Pouta A, Bloigu A, et al. Immediate complications after medical compared with surgical termination of pregnancy. *Obstet Gynecol.* 2009;114(4):795-804.

¹²⁴ Ireland LD, Gatter, M, Chen, A. 2015. Medical Compared with Surgical Abortion for Effective Pregnancy Termination in the First Trimester. *Obstetrics & Gynecology* 126:22-28.

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Unanticipated aspiration for persistent pain, bleeding or both were 1.8 percent and 0.4 percent for medical and surgical abortion respectively. These findings are compatible with the Niinimäki study findings. There was no difference in major adverse events as defined by the authors (emergency department visit, hospitalization, uterine perforation, infection, hemorrhage requiring transfusion) between the groups. The authors conclude medical and surgical abortion before 64 days of gestation are both highly effective with low complication rates.

The 2018 Carlsson study is addressed above in section II.A.2.b.ii. of this response; as discussed above, that study showed no statistically significant difference between the overall complication rates between an “at home” and “at the hospital” abortion.¹²⁵

We acknowledge that medical abortion is known to have more days of bleeding and increased rates of incomplete abortion compared to surgical abortion. However, as noted above, in the vast majority of medical abortions, surgical intervention is not necessary. Thus, medical abortion and surgical abortion are two options; both have benefits, side effects, and potential complications. Patients and their healthcare providers should discuss which method is preferable and safer according to each woman’s unique situation.

You state that the Mifeprex REMS should require a formal study for at-risk populations, including: patients under the age of 18; patients with repeat Mifeprex abortions; patients with limited access to emergency room services; and patients who self-administer misoprostol (Petition at 13-14). As we explain below, additional studies are not needed at this time.

In justifying your assertion that a formal study is required in patients under the age of 18, you state that Mifeprex was approved for use in the pediatric population in 2000 after the requirement for studies in the pediatric population was waived (Petition at 13-14). The approved indication for mifepristone does not limit its use by age. Although patients age 17 and under were not included in the clinical trials supporting the initial approval of Mifeprex in 2000, we stated at the time that the safety and efficacy were expected to be the same for postpubertal (i.e., post-menarchal) adolescents. Our conclusion in 2000 that pediatric studies of Mifeprex were not needed for approval was consistent with FDA’s implementation of the regulations in effect at that time. Because we determined that there were sufficient data from studies of mifepristone, the original Mifeprex approval should have reflected the Agency’s conclusion that the pediatric study requirements were waived for pre-menarchal females and that the pediatric study requirements were met for post-menarchal adolescents, rather than stating that the Agency was waiving the requirements for all pediatric age groups.

As currently required by the Pediatric Research Equity Act (PREA),¹²⁶ certain applications or supplemental applications must include pediatric assessments of the safety and effectiveness of the drug for the claimed indication(s) in all relevant pediatric

¹²⁵ Carlsson et al., *supra* n. 49.

¹²⁶ Section 505B of the FD&C Act (21 U.S.C. 355c).

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subpopulations, unless that requirement is waived or deferred.¹²⁷ In accordance with PREA, when FDA reviewed the S-020 efficacy supplement, a partial waiver was granted for pediatric studies in pre-menarchal females because pregnancy does not occur in premenarchal females. We also determined that the applicant had fulfilled the pediatric study requirement in post-menarchal adolescents. This determination was based on data extrapolated from adults and information in literature. Review of these findings found the safety and efficacy in this population to be similar to the safety and efficacy in the adult population.¹²⁸ Therefore, we do not agree that a formal study is required in patients under 18.

With regard to your concerns about repeat abortions and your assertion that a study is necessary in this population, we acknowledge that published data concerning adverse reproductive health outcomes in U.S. women who undergo repeat medical abortions are limited. We concluded in our 2016 review of the S-020 efficacy supplement that there is no evidence that repeated medical or surgical abortion is unsafe or that there is a tolerance effect. We also noted that return to fertility after the use of mifepristone is well documented.¹²⁹ This is reflected both in Section 17 of the approved labeling, Patient Counseling Information, which states that the provider should “inform the patient that another pregnancy can occur following medical abortion and before resumption of normal menses,” and in the Medication Guide, which states “You can become pregnant again right after your pregnancy ends.” Although you state that more than one out of every three abortions in the United States is a repeat abortion (Petition at 14),¹³⁰ we are not aware of reports suggesting greater safety concerns in repeat abortions than a first-time abortion. Therefore, we do not agree that a study is necessary in this population. You also cite a published study, using a mouse model, of repeated medical termination of pregnancy that showed repeat medical abortion impaired the reproductive function of female mice (Petition at 14).¹³¹ Per our 2016 review, there is no evidence in available clinical data that repeated medical or surgical abortion is unsafe, or that fertility is impaired by the use of mifepristone; therefore, data from a single non-clinical study in mice are not persuasive.¹³²

With respect to your request for a formal study of mifepristone for medical abortion in women without access to emergency care, we disagree that such a study is necessary. In order to become a certified prescriber, a healthcare provider must agree that they have the ability to provide surgical intervention in cases of incomplete abortion or severe bleeding or have made plans to provide such care through others, and that they have the ability to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary. These prescriber qualifications ensure that mifepristone is prescribed to women for whom emergency care is available.

¹²⁷ Section 505B(a)(2) of the FD&C Act (21 U.S.C. 355c(a)(2)).

¹²⁸ 2016 Clinical Review, *supra* n. 13, at 74-76.

¹²⁹ *Id.* at 47.

¹³⁰ In support of this assertion, you cite Jones R, Jerman J, Ingerick M. Which abortion patients have had a prior abortion? Findings from the 2014 U.S. Abortion Patient Survey. *J Womens Health*.

¹³¹ Lv F, Xu X, Zhang S, et al. Repeated abortion affects subsequent pregnancy outcomes in BALB/c mice. *PLoS One*. 2012;7(10):e48384. doi:10.1371/journal.pone.0048384.

¹³² 2016 Clinical Review, *supra* n. 13, at 47.

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Finally, you assert that FDA should require a formal study in patients who self-administer misoprostol. As explained in section II.A.2.b.ii of this response, FDA conducted a literature review of self-administration of misoprostol at home as part of its review of the S-020 efficacy supplement and found no safety or efficacy concerns with home self-administration of misoprostol. Therefore, we disagree that a formal study is required in this population.

With regard to safety generally, in addition to the FAERS data provided above (see section II.B.1.c.ii. in this response), FDA routinely monitors adverse events reported to FAERS and published in the medical literature for mifepristone for medical termination of pregnancy through 70 days gestation. We have not identified any new safety concerns with the use of mifepristone for this indication.

3. Other Articles

In your Petition, you reference several documents that discuss alternative models of providing abortion medications and advocate for the lifting of the REMS on mifepristone (Petition at 23-24). You assert that these recent publications demonstrate how abortion advocates will continue to pressure FDA to eliminate the REMS and move towards over-the-counter access for Mifeprex.¹³³

We agree that the overarching message in the publications you reference appears to be advocating self-management of medical abortion. Nonetheless, as discussed in this response, we have determined that the Mifepristone REMS Program continues to be necessary for the safe use of this drug product, with some modifications.

III. CONCLUSION

For the reasons set forth above, we deny your request that FDA restore and strengthen elements of the Mifeprex regimen and prescriber requirements approved in 2000; and we grant in part and deny in part your request to retain the Mifepristone REMS Program. As with all approved drug products, we will continue to monitor the safety of mifepristone for the approved indication and take any appropriate actions.

Sincerely,

Patrizia A.
Cavazzoni -S

Digitally signed by Patrizia A.
Cavazzoni -S
Date: 2021.12.16 15:05:41 -05'00'

Patrizia Cavazzoni, M.D.
Director
Center for Drug Evaluation and Research

¹³³ You also reference clinical trials relating to the use of mifepristone for spontaneous miscarriage management and question the results of studies related to this use (Petition at 16-18). The use of mifepristone for the management of early miscarriage is not an approved indication for this drug product and is outside the scope of the Mifepristone REMS Program. Therefore, we do not address it in this response.

EXHIBIT E



NDA 020687

REMS MODIFICATION NOTIFICATION

Danco Laboratories, LLC

(b) (4), (b) (6)

P.O. Box 4816
New York, NY 10185

Dear (b) (4), (b) (6):

We refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Mifeprex (mifepristone) Tablets.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for mifepristone was originally approved on June 8, 2011, and your single shared system REMS (SSS REMS) was approved on April 11, 2019. Your last SSS REMS modification was approved May 14, 2021. The SSS REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

In accordance with section 505-1(g)(4)(B) of the Federal Food, Drug, and Cosmetic Act (FDCA), we have determined that your approved REMS for mifepristone must be modified to minimize the burden on the healthcare delivery system of complying with the REMS and to ensure that the benefits of the drug outweigh the risks.

This determination is based on a review of published literature, safety information collected during the COVID-19 PHE, FDA Adverse Event Reporting System (FAERS) reports, REMS assessment reports, and information provided by advocacy groups, individuals, the Applicants, and plaintiffs in ongoing litigation.

Your approved REMS must be modified as follows:

Elements to Assure Safe Use: We have determined that the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (i.e., the “in-person dispensing requirement”) is no longer necessary to ensure the benefits of mifepristone outweigh the risks of serious complications associated with mifepristone that are listed in the labeling of the drug. Removal of the requirement for in-person dispensing will also minimize the burden on the healthcare delivery system of complying with the REMS.

Elements to Assure Safe Use: Pursuant to 505-1(f)(1), we have also determined that an additional element to assure safe use is necessary to mitigate the risk of serious

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complications associated with mifepristone listed in the labeling of the drug. Modification of the Mifepristone REMS to allow dispensing of mifepristone by pharmacies requires the addition of certification of pharmacies that dispense the drug.

Your REMS must include elements to mitigate this risk, including at least the following:

- Healthcare providers have particular experience or training, or are specially certified
- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified
- The drug is dispensed to patients with evidence or other documentation of safe use conditions.

The REMS must include an implementation system to monitor, evaluate, and work to improve the implementation of the elements to assure safe use (outlined above). Include an intervention plan to address any findings of non-compliance with the ETASU.

The proposed REMS must include a timetable for submission of assessments. The proposed REMS modification submission should include a new proposed REMS document and appended REMS materials, as appropriate, that show the complete previously approved REMS with all proposed modifications highlighted and revised REMS materials.

In addition, the submission should also include an update to the REMS supporting document that includes a description of all proposed modifications and their potential impact on other REMS elements. Revisions to the REMS supporting document should be submitted with all changes marked and highlighted.

Because we have determined that a REMS modification as described above is necessary to minimize the burden on the health care delivery system of complying with the REMS, and to ensure that the benefits of the drug outweigh the risks, you must submit a proposed REMS modification within 120 days of the date of this letter.

Submit the proposed modified REMS as a Prior Approval supplement (PAS) to your NDA.

NDA 020687

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Because FDA is requiring the REMS modifications in accordance with section 505-1(g)(4)(B), you are not required to submit an adequate rationale to support the proposed modifications, as long as the proposals are consistent with the modifications described in this letter. If the proposed REMS modification supplement includes changes that differ from the modifications described in this letter, an adequate rationale is required for those additional proposed changes in accordance with section 505-1(g)(4)(A).

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

**NEW SUPPLEMENT FOR NDA 020687/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION**

Prominently identify subsequent submissions related to the proposed REMS modification with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 020687/S-000
PROPOSED REMS MODIFICATION-AMENDMENT**

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

In addition to submitting the proposed modified REMS as described above, you can also submit the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, include the SPL file with your proposed REMS modification submission.

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

NDA 020687

Page 4

If you have any questions, call (b) (6), at (b) (6).

Sincerely,

{See appended electronic signature page}

(b) (6)

Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

(b) (6)

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EXHIBIT F



ANDA 091178

REMS MODIFICATION NOTIFICATION

GenBioPro, Inc.

(b) (4), (b) (6)

Dear (b) (4), (b) (6) :

Please refer to your Abbreviated New Drug Application (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for mifepristone tablets.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The Shared System (SS) REMS for mifepristone consists of elements to assure safe use, and an implementation system.

In accordance with section 505-1(g)(4)(B) of the FD&C Act, we have determined that your approved REMS for mifepristone must be modified to minimize the burden on the health care delivery system of complying with the REMS and to ensure that the benefits of the drug outweigh the risks.

This determination is based on a review of published literature, safety information collected during the COVID-19 PHE, FDA Adverse Event Reporting System (FAERS) reports, REMS assessment reports, and information provided by advocacy groups, individuals, the Applicants, and plaintiffs in ongoing litigation.

Your approved REMS must be modified as follows:

Elements to Assure Safe Use: We have determined that the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (i.e., the “in-person dispensing requirement”) is no longer necessary to ensure the benefits of mifepristone outweigh the risks of serious complications associated with mifepristone that are listed in the labeling of the drug. Removal of the requirement for in-person dispensing will reduce the burden on the healthcare delivery system of complying with the REMS.

Elements to Assure Safe Use: Pursuant to 505-1(f)(1), we have also determined that an additional element to assure safe use is necessary to mitigate the risk of

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20903
www.fda.gov

serious complications associated with mifepristone listed in the labeling of the drug. Modification of the Mifepristone REMS to allow dispensing of mifepristone by pharmacies requires the addition of certification of pharmacies that dispense the drug.

Your REMS must include elements to mitigate this risk, including at least the following:

- Healthcare providers who prescribe the drugs have particular experience or training, or are specially certified
- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified
- The drug is dispensed to patients with evidence or other documentation of safe use conditions

The REMS must include an implementation system to monitor, evaluate, and work to improve the implementation of the ETASU (as outlined above). Include an intervention plan to address any findings of non-compliance with the ETASU.

The proposed REMS modification submission should include a new proposed REMS document and appended REMS materials, as appropriate, that show the complete previously approved REMS with all proposed modifications highlighted and revised REMS materials.

In addition, the submission should also include an update to the REMS supporting document that includes a description of all proposed modifications and their potential impact on other REMS elements. Revisions to the REMS supporting document should be submitted with all changes marked and highlighted.

Because we have determined that a REMS modification as described above is necessary to minimize the burden on the health care delivery system of complying with the REMS and to ensure that the benefits of the drug outweigh the risks, you must submit a proposed REMS modification within 120 days of the date of this letter.

Submit the proposed modified REMS as a Prior Approval supplement (PAS) to your ANDA.

Because FDA is requiring the REMS modifications in accordance with section 505-1(g)(4)(B) of the FD&C Act, you are not required to submit an adequate rationale to support the proposed modifications, as long as the proposals are consistent with the modifications described in this letter. If the proposed REMS modification supplement includes changes that differ from the modifications described in this letter, an adequate rationale is required for those additional proposed changes in accordance with section 505-1(g)(4)(A) of the FD&C Act.

ANDA 091178
Page 3

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

**NEW SUPPLEMENT FOR ANDA 091178/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION**

Prominently identify subsequent submissions related to the proposed REMS modification with the following wording in bold capital letters at the top of the first page of the submission:

**ANDA 091178/S-000
PROPOSED REMS MODIFICATION-AMENDMENT**

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

In addition to submitting the proposed modified REMS as described above, you can also submit the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, include the SPL file with your proposed REMS modification submission.

For more information on submitting REMS in SPL format, please email REMS_Website@fda.hhs.gov.

If you have any questions, call

(b) (6)

.

Sincerely,

{See appended electronic signature page}

(b) (6)

Center for Drug Evaluation and Research

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20903
www.fda.gov

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

(b) (6)

12/16/2021 03:21:22 PM

EXHIBIT G

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020687Orig1s025

SUMMARY REVIEW

(b) (6) and (b) (6)
 (b) (6)
 (b) (6)
 Center for Drug Evaluation and Research (CDER)

Application Type	NDA and ANDA
Application Number	NDA 020687 and ANDA 091178
Supplement Number, Date Received	NDA Supplement-025 and ANDA Supplement-004 received June 22, 2022 (sequences 18 and 87 respectively) and amended October 19, 2022 (sequences 22 and 91 respectively), November 30, 2022 (sequences 24 and 92 respectively), December 9, 2022 (sequences 25 and 93 respectively) and December 16, 2022 (sequences 26 and 95 respectively). This supplement is on a 180-Day clock.
Targeted Action Date	December 19, 2022
(b) (6) #	2022-1169
Reviewer Names	(b) (6) (b) (6) (b) (6)
(b) (6)	(b) (6) (b) (6)
(b) (6)	(b) (6)
(b) (6)	(b) (6)
(b) (6)	(b) (6)
Review Completion Date	January 3, 2023
Subject	Review of proposed Major REMS Modification
Established Name	Mifepristone REMS
Name of Sponsor	Danco Laboratories, LLC and GenBioPro, Inc.
Therapeutic Class	Progestin antagonist
Formulation	Oral tablet

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EXECUTIVE SUMMARY

This is a review of the proposed modification to the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone 200 mg (hereafter referred to as the Mifepristone REMS Program) submitted by Danco Laboratories, LLC (Danco) for new drug application (NDA) 020687 and by GenBioPro, Inc. (GBP) for abbreviated new drug application (ANDA) 091178. The Sponsors submitted proposed modification to the Mifepristone REMS Program on June 22, 2022, and amended their submissions on October 19, 2022 (Danco), October 20, 2022 (GBP), November 30, 2022 (both), December 9, 2022 (both) and December 16, 2022 (both).

The Mifepristone REMS Program was originally approved on April 11, 2019, to mitigate the risk of serious complications associated with mifepristone 200 mg. The most recent REMS modification was approved on May 14, 2021.^a The Mifepristone REMS Program consists of elements to assure safe use (ETASU) A, C and D, an implementation system, and a timetable for submission of assessments of the REMS.

The Sponsors submitted the proposed modification to the REMS in response to the Agency's REMS Modification Notification letters dated December 16, 2021, which required removal of the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (i.e., the "in-person dispensing requirement") and the addition of certification of pharmacies that dispense the drug.

In addition, the following were addressed during the course of the review:

- revisions to the REMS goal to align with the updated REMS requirements.
- replacing serial number with recording of NDC and lot number of mifepristone dispensed.
- additional edits for clarification and consistency in the REMS Document and REMS materials (*Prescriber Agreement Forms, Patient Agreement Form, and Pharmacy Agreement Forms*).

The review team finds the proposed modification to the Mifepristone REMS Program last submitted on December 16, 2022, to be acceptable and recommends approval of the REMS modification. The proposed REMS modification includes changes to the REMS goal, additional REMS requirements for prescribers to incorporate dispensing from certified pharmacies and new REMS requirements for pharmacy certification.

The proposed goal of the modified REMS for mifepristone 200 mg is to mitigate the risk of serious complications associated with mifepristone by:

- a) Requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program.
- b) Ensuring that mifepristone is only dispensed by or under the supervision of certified prescribers, or by certified pharmacies on prescriptions issued by certified prescribers.
- c) Informing patients about the risk of serious complications associated with mifepristone.

^a The May 14, 2021 REMS modification approved the inclusion of gender neutral language in the Patient Agreement Form as well as corresponding minor changes to the REMS document to be consistent with the changes made to the Patient Agreement Form.

The timetable for submission of assessments of the REMS was modified to one year from the date of the approval of the modified REMS and annually thereafter. The assessment plan was revised to align with the changes to the REMS and capture additional metrics for drug utilization and REMS operations.

The modified REMS includes ETASU A, B and D, an implementation system, and a timetable for submission of assessments of the REMS. Mifepristone will no longer be required to be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (referred to as the “in-person dispensing requirement” for brevity) and will be able to be dispensed from certified pharmacies.

1. Introduction

This review evaluates the proposed modification to the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone 200 mg (hereafter referred to as the Mifepristone REMS Program) submitted by Danco Laboratories, LLC (Danco) for new drug application (NDA) 020687 and by GenBioPro, Inc. (GBP) for abbreviated new drug application (ANDA) 091178.

The Sponsors initially submitted proposed modification to the Mifepristone REMS Program on June 22, 2022, in response to the Agency’s REMS Modification Notification letters issued on December 16, 2021, to Danco and GBP, requiring the following modification to minimize the burden on the healthcare delivery system of complying with the REMS and to ensure that the benefits of the drug outweigh the risks:

- removal of the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (i.e., the “in-person dispensing requirement”)
- addition of certification of pharmacies that dispense the drug

Per the Agency’s December 16, 2021, REMS Modification Notification letters, the proposed REMS was required to include the following ETASU to mitigate the risk of serious complications associated with mifepristone, including at least the following:

- healthcare providers have particular experience or training, or are specially certified
- pharmacies, practitioners, or health care settings that dispense the drug are specially certified
- the drug is dispensed to patients with evidence or other documentation of safe use conditions

The REMS was also required to include an implementation system and timetable for submission of assessments.

2. Background

2.1. Product Information and REMS Information

Mifepristone is a progestin antagonist indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy (IUP) through 70 days gestation. Mifepristone is available as 200 mg tablets for oral use.

Mifeprex (mifepristone) was approved on September 28, 2000, with a restricted distribution program under 21 CFR 314.520 (subpart H)^b to ensure that the benefits of the drug outweighed

^b NDA approval letter Mifeprex (NDA 020687) dated September 28, 2000.

the risk of serious complications associated with mifepristone when used for medical abortion.^c Mifeprex was deemed to have in effect an approved REMS under section 505-1 of the Federal Food, Drug, and Cosmetic Act with the passage of the Food and Drug Administration Amendments Act of 2007 (FDAAA), and the Mifeprex REMS was approved on June 8, 2011.

On March 29, 2016, FDA approved an efficacy supplement for Mifeprex, which included changes in the dose of Mifeprex and the dosing regimen for taking Mifeprex and misoprostol, as well as a modification of the gestational age up to which Mifeprex has been shown to be safe and effective and a modification to the process for follow-up after administration of the drug. FDA also approved modification to the Mifeprex REMS that reflected the changes approved in the efficacy supplement.¹⁻⁵ On April 11, 2019, FDA approved ANDA 091178 and the Mifepristone REMS Program.⁶⁻⁷ The Mifepristone REMS Program is a single, shared system REMS that includes NDA 020687 and ANDA 091178. The goal of the approved Mifepristone REMS Program is to mitigate the risk of serious complications associated with mifepristone by:

- a) Requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program (under ETASU A).
- b) Ensuring that mifepristone is only dispensed in certain healthcare settings by or under the supervision of a certified prescriber (under ETASU C).
- c) Informing patients about the risk of serious complications associated with mifepristone (under ETASU D).

The Mifepristone REMS Program was last modified and approved in 2021 to revise the *Patient Agreement Form* to include gender-neutral language; however, the goal of the Mifepristone REMS Program has not changed since the initial approval in 2019.

Under ETASU A, to become specially certified to prescribe mifepristone, a healthcare provider must review the prescribing information, complete and sign the *Prescriber Agreement Form*, and agree to follow the guidelines for use of mifepristone. Under ETASU C, in the Mifepristone REMS Program as approved prior to today's action, mifepristone was required to be dispensed to patients only in certain healthcare settings, specifically clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber. Under ETASU D, mifepristone must be dispensed to patients with evidence or other documentation of safe use conditions (i.e., the patient must sign a *Patient Agreement Form*). The approved Mifepristone REMS Program includes an implementation system, and a timetable for assessments (one year from the date of the initial approval of the REMS on April 11, 2019, and every three years thereafter).

In April 2021, FDA communicated its intent to exercise enforcement discretion during the COVID-19 public health emergency (PHE) regarding the in-person dispensing requirement in the Mifepristone REMS Program. Specifically, FDA communicated that provided all other requirements of the Mifepristone REMS Program are met, the Agency intended to exercise enforcement discretion with respect to the in-person dispensing requirement of the Mifepristone REMS Program, including any in-person requirements that may be related to the *Patient Agreement Form*, during the COVID-19 PHE. This determination, which FDA made on April 12, 2021, was effective immediately. We also note that from July 13, 2020, to January 12, 2021, per a court order, FDA was enjoined from enforcing the in-person dispensing requirement of the Mifepristone REMS Program.⁸

^c Mifepristone is also approved in approximately 80 other countries.
https://gynuity.org/assets/resources/biblio_ref_lst_mife_en.pdf

Further, and as we also communicated on April 12, 2021, to the extent all of the other requirements of the Mifepristone REMS Program are met, the Agency intended to exercise enforcement discretion during the COVID-19 PHE with respect to the dispensing of Mifeprex or the approved generic version of Mifeprex, Mifepristone Tablets, 200 mg, through the mail, either by or under the supervision of a certified prescriber, or through a mail-order pharmacy when such dispensing is done under the supervision of a certified prescriber.

2.2. Regulatory History

The following is a summary of the regulatory history relevant to this review:

- 04/11/2019: Approval of the Mifepristone REMS Program, a single, shared system REMS that includes NDA 020687 and ANDA 091178.
- 04/12/2021: The Agency issued a General Advice letter to both the NDA and ANDA Applicants, explaining that FDA intended to exercise enforcement discretion during the COVID-19 PHE with respect to the in-person dispensing requirement in the Mifepristone REMS Program, including any in-person requirements that may be related to the Patient Agreement Form.
- 05/07/2021: The Agency stated that it would be reviewing the elements of the Mifepristone REMS Program in accordance with section 505-1 of the FD&C Act.
- 12/16/2021: The Agency completed its review of the Mifepristone REMS Program and determined, among other things, that the REMS must be modified to remove the in-person dispensing requirement and add pharmacy certification.⁹
- 12/16/2021: REMS Modification Notification letters were sent to both Sponsors stating that the approved Mifepristone REMS Program must be modified to minimize the burden on the healthcare system of complying with the REMS and ensure that the benefits of the drug outweigh the risks.
- 04/08/2022: Final written responses to a Type A meeting request were provided to Danco, the point of contact for the Mifepristone REMS Program. The questions pertained to the 12/16/2021 REMS Modification Notification letter requirements.
- 04/13/2022: The Sponsors requested an extension to 6/30/2022, to submit a proposed REMS modification in response to the Agency's 12/16/2021 REMS Modification Notification letters.
- 04/15/2022: The Agency granted the Sponsors' request for an extension to submit a proposed REMS modification and conveyed that the modification must be submitted no later than 06/30/2022.¹⁰
- 06/22/2022: Danco and GBP submitted a proposed REMS modification to their respective applications in response to the 12/16/2021 REMS Modification Notification letters.
- 07/22/2022: An Information Request was sent to the Sponsors requesting clarification of the proposed prescriber and dispenser requirements and additional rationale to support their proposal.
- 08/26/2022: Sponsors submitted responses to 07/22/2022 Information Request.
- 09/19/2022: Teleconference was held between Agency and Sponsors where the Agency communicated the REMS requirements that are necessary to support the addition of pharmacy

certification. The Agency proposed focusing on the pharmacy settings where a closed system^d REMS could be implemented using the existing email and facsimile based system, (b) (4), as the best strategy for an approvable modification by the goal date.

- 09/22/2022: An Information Request was sent to Sponsors requesting confirmation that the Sponsors agree with the pharmacy distribution approach outlined in the 09/19/2022 teleconference so that the Agency's feedback could be appropriately tailored.
- 09/23/2022: The Sponsors confirmed via email that they were willing to pursue (b) (4), as discussed in the 09/19/2022 teleconference. The Sponsors also requested a teleconference to discuss the current modification (b) (4).
- 09/27/2022: Comments from the 09/19/2022 teleconference sent to Sponsors with additional comments and requests regarding what will be necessary for pharmacy certification.
- 09/29/2022: An Information request was sent to the Sponsors asking for agenda items, questions, and a request to walk through their proposed system for pharmacy certification, including dispensing through mail-order or specialty pharmacies, at the 10/06/2022 scheduled teleconference.
- 10/04/2022: Sponsors emailed that they will focus the 10/06/2022 teleconference on the 09/27/2022 Agency comments and their mail order and specialty pharmacy distribution model.
- 10/06/2022: Teleconference was held between Agency and Sponsors where Sponsors outlined their proposal for pharmacy certification, including dispensing through mail order and specialty pharmacies, as well as their concerns with certain requirements and general timelines.
- 10/19/2022: Danco submitted a REMS amendment to their pending sNDA, which included a REMS document and REMS materials. They did not submit a REMS Supporting Document.
- 10/20/2022: GBP submitted a REMS amendment to their pending sANDA, which included a REMS document and REMS materials. They did not submit a REMS Supporting Document.
- 10/25/2022: Teleconference was held between Agency and Sponsors to discuss the *Patient Agreement Form* and timing related to shipping a mifepristone prescription from a certified pharmacy to the patient.
- 11/23/2022: An Information Request was sent to Sponsors with comments on their proposed REMS Document, submitted on 10/19/2022 (Danco) and 10/20/2022 (GBP).
- 11/30/2022: Danco and GBP submitted REMS amendments, which included the REMS Document, to their respective pending supplemental applications.
- 12/01/2022: Teleconference was held between Agency and Sponsors to discuss the REMS Document.
- 12/05/2022: An Information Request was sent to Sponsors with comments on their proposed REMS Document submitted on 11/30/2022 and discussed at the teleconference on 12/01/2022, and REMS materials submitted to their applications on 10/19/2022 and 10/20/2022.

^d "Closed system" in this case refers to a system where prescribers, pharmacies, and distributors are certified or authorized in the REMS and the certification of the stakeholder must be verified prior to distribution or dispensing, as per the REMS.

- 12/07/2022: Teleconference was held between Agency and Sponsors to discuss the REMS Document and REMS materials the Agency sent to the Sponsors on 12/05/22.
- 12/08/2022: Danco and GBP submitted REMS amendments, including the REMS Document, *Prescriber Agreement Form*, *Pharmacy Agreement Form*, *Patient Agreement Form* and REMS Supporting Document, to their respective pending applications.
- 12/09/2022: An Information Request was sent to Sponsors with the Agency's comments on the REMS assessment plan.
- 12/14/2022: An Information Request was sent to Sponsors with the Agency's comments on the REMS Document, *Prescriber Agreement Form*, *Pharmacy Agreement Form*, and REMS Supporting Document.
- 12/15/2022: Two teleconferences were held between Agency and Sponsors to discuss the proposed REMS Document and REMS materials the Agency sent to the Sponsors on 12/14/22.
- 12/16/2022: Sponsors submitted a REMS amendment to their respective applications.

3. Review of Proposed REMS Modification

(b) (6) has discussed the Sponsors' proposed modification with the review team, which includes members of the (b) (6) and the (b) (6); hereafter referred to as the review team. This review includes their input and concurrence with the analysis and proposed changes to the Mifepristone REMS Program.

3.1. REMS Goal

The Sponsors proposed modification to the goal for the Mifepristone REMS Program to add that mifepristone can also be dispensed from certified pharmacies on prescriptions issued by certified prescribers. The proposed REMS goal is:

The goal of the REMS for mifepristone is to mitigate the risk of serious complications associated with mifepristone by:

- a) Requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program.
- b) Ensuring that mifepristone is only dispensed by or under the supervision of certified prescribers, or by certified pharmacies on prescriptions issued by certified prescribers.
- c) Informing patients about the risk of serious complications associated with mifepristone.

Reviewer Comment: *We agree with the Sponsors' proposal.*

3.2. REMS Document

The proposed REMS Document is not in the format as outlined in the 2017 Draft Guidance for Industry, Format and Content of a REMS Document.¹¹

Reviewer Comment: To avoid the misperception that this REMS modification is making major changes to the REMS document that go beyond our December 16, 2021, determination that the REMS must be modified to remove the in-person dispensing requirement and add pharmacy certification, CDER staff and management discussed whether to change the format of the REMS document to that described in the 2017 draft guidance.¹¹ After internal discussion, CDER staff and management aligned not to transition the REMS document at this time to the format described in the 2017 draft guidance.

3.3. REMS Requirements

3.3.1. Addition and Removal of ETASU

The December 16, 2021, REMS Modification Notification letters specified that the ETASU must be modified to minimize the burden on the healthcare delivery system of complying with the REMS and to ensure the benefits of the drug outweigh the risks by:

- Removing the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices and hospitals (i.e., the “in-person dispensing requirement”), and;
- Adding a requirement that pharmacies that dispense the drug be specially certified.

The Sponsors proposed changes to the REMS as reflected in the subsections below.

3.3.2. REMS Participant Requirements and Materials

3.3.2.1. Prescriber Requirements

Consistent with the approved Mifepristone REMS Program prescribers must be specially certified. To become specially certified to prescribe mifepristone, healthcare providers who prescribe must review the Prescribing Information for mifepristone and complete the *Prescriber Agreement Form*. In signing the *Prescriber Agreement Form*, prescribers agree they meet certain qualifications and will follow the guidelines for use of mifepristone. The guidelines for use include ensuring i) that the *Patient Agreement Form* is reviewed with the patient and the risks of the mifepristone treatment regimen are fully explained; ii) that the healthcare provider (HCP) and the patient sign the *Patient Agreement Form*, iii) the patient receives a copy of the *Patient Agreement Form* and Medication Guide, iv) the *Patient Agreement Form* is placed in the patient’s medical record; v) that any patient deaths are reported to the Mifepristone Sponsor that provided the mifepristone, identifying the patient by a non-identifiable reference and including the NDC and lot number from the package of mifepristone that was dispensed to the patient. The language on the guidelines for use was revised from the Mifepristone REMS Program approved in 2021 to clarify that, if the certified prescriber supervises the dispensing of mifepristone, they must ensure the guidelines for use of mifepristone are followed by those under their supervision. This clarification reflects the ongoing implementation of the approved Mifepristone REMS Program. For example, consistent with the approved REMS, the *Patient Agreement Form* does not require the certified prescriber’s signature, but rather the signature of the healthcare provider counseling the patient on the risks of mifepristone. Additional changes were made globally to provide consistency and clarity of the requirements for certified prescribers and healthcare providers who complete tasks under the supervision of certified prescribers.

A certified prescriber may submit the *Prescriber Agreement Form* to an authorized distributor if the certified prescriber wishes to dispense or supervise the dispensing of mifepristone; this is consistent with the current requirements of the Mifepristone REMS Program. Additional requirements were

added to incorporate mifepristone dispensing by a certified pharmacy. If a healthcare provider wishes to prescribe mifepristone by sending a prescription to a certified pharmacy for dispensing, the healthcare provider must become certified by providing the pharmacy a *Prescriber Agreement Form* signed by the provider. A certified prescriber must also assess the appropriateness of dispensing mifepristone when contacted by a certified pharmacy about patients who will receive mifepristone more than four calendar days after the prescription was received by the certified pharmacy.

The NDC and lot number of the dispensed drug will be recorded in the patient's record when mifepristone is dispensed by or under the supervision of a certified prescriber, replacing the requirement that serial numbers from each package of mifepristone be recorded in the patient's record. If prescribers become aware of the death of a patient for whom the mifepristone was dispensed from a certified pharmacy, the prescribers will be required to obtain the NDC and lot number of the package of mifepristone the patient received from the pharmacy.

The following materials support prescriber requirements:

- *Prescriber Agreement Form* for Danco Laboratories, LLC
- *Prescriber Agreement Form* for GenBioPro, Inc.
- *Patient Agreement Form*

Reviewer Comment: *We agree with the Sponsors' proposal.*

Although certain activities (review of the Patient Agreement Form with patients and answering any questions about treatment, signing, providing a copy to the patient and retaining the Patient Agreement Form, providing a copy of the Medication Guide, and ensuring any deaths are reported to the Mifepristone Sponsor, recording the NDC and lot number from drug dispensed from the certified prescriber or those under their supervision) may be conducted by healthcare providers under the supervision of a certified prescriber, the certified prescriber remains responsible for ensuring compliance with the requirements of the Mifepristone REMS Program. We agree with the additional language to further clarify that the certified prescriber must ensure the guidelines for use of mifepristone are followed.

As proposed, certified prescribers may either, 1) continue to submit the Prescriber Agreement Form to an authorized distributor if the certified prescriber is dispensing or supervising the dispensing of the drug (as already required in the REMS), or 2) if the drug will be dispensed from a certified pharmacy, submit the Prescriber Agreement Form to the certified pharmacy that will dispense the drug (as proposed in the modification). Regarding #2, the pharmacy can only fill prescriptions written by a certified prescriber.

Based on our review of the proposed changes, the review team finds it acceptable for prescribers to submit their Prescriber Agreement Form directly to the certified pharmacy. Although certified prescribers still have the option of in-person dispensing of the drug, not all prescribers may want to stock mifepristone. Typically due to the number of drugs that are available and the expense associated with stocking prescription medications intended for outpatient use, most prescribers do not stock many medications, if they stock medications at all.

The proposal to submit a Prescriber Agreement Form to a certified pharmacy provides another option for dispensing mifepristone. The burden of providing the Prescriber Agreement Form prior to or when the prescription is provided to a certified pharmacy does not create unreasonable burden for prescribers. The burden of prescriber certification has been minimized to the extent possible. The Prescriber Agreement Form is designed to require minimal time to complete and requires that the prescriber submit it to the authorized distributor once, and if the prescriber chooses to use a certified pharmacy to dispense mifepristone, they will need to submit the form to the certified pharmacy.

There is an additional requirement added for certified pharmacies and certified prescribers in the event that a patient will not receive their medication from the certified pharmacy within four calendar days of the pharmacy's receipt of the prescription (for example, if the medication is not in stock). In this circumstance, the pharmacy will be required to contact the certified prescriber to make them aware of the delay and will be required to obtain from the prescriber confirmation that it is appropriate to dispense mifepristone to the patient even though they will receive mifepristone more than four calendar days after the prescription was received by the certified pharmacy. This confirmation is intended to ensure timeliness of delivery in light of the labeled indication and gestational age. Additional details and rationale on the pharmacy requirements to dispense and ship drug in a timely manner are described in section 3.3.2.3.

If a certified prescriber becomes aware of a patient death that occurs subsequent to the use of mifepristone dispensed from a pharmacy, the certified prescriber must obtain the NDC and lot number of the package of mifepristone the patient received from the pharmacy. This information will be reported to the appropriate Mifepristone Sponsor in the same manner prescribers have done previously. This additional requirement to obtain the NDC and lot number from the pharmacy is needed to ensure consistent adverse event reporting when mifepristone is dispensed from a certified pharmacy.

Prescriber Agreement Form

The Sponsors' proposed changes to the *Prescriber Agreement Form* aligned with those described above. The proposed *Prescriber Agreement Form* explains the two methods of certification which are: 1) submitting the form to the authorized distributor and 2) submitting the form to the dispensing certified pharmacy. Further clarification was added that healthcare settings, such as medical offices, clinics, and hospitals, where mifepristone will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification. The statement that certified prescribers are responsible for overseeing implementation and compliance with the REMS Program was also added. The following statement was added to the form: "I understand that the pharmacy may dispense mifepristone made by a different manufacturer than that stated on the Prescriber Agreement Form." The account set up information was removed and replaced with prescriber information response fields.

Reviewer Comment: *We agree with the Sponsors' proposal. Changes in the above prescriber requirements were incorporated in the Prescriber Agreement Form.*

3.3.2.2. Patient Requirements

The *Patient Agreement Form* was updated to clarify that the signatures may be written or electronic, to reorganize the risk information about ectopic pregnancy, and to remove the statement that the Medication Guide will be taken to an emergency room or provided to a healthcare provider who did not prescribe mifepristone so that it is known that the patient had a medical abortion with mifepristone.

The following materials support patient requirements:

- *Patient Agreement Form*

Reviewer Comment: *We agree with the Sponsors' proposal.*

The Patient Agreement Form continues to be an important part of standardizing the medication information on the use of mifepristone that prescribers communicate to their patients, and also provides the information in a brief and understandable format for patients. The requirement to counsel the

patient, to provide the patient with the Patient Agreement Form, and to have the healthcare provider and patient sign the Patient Agreement Form, ensures that each provider, including new providers, informs each patient of the appropriate use of mifepristone, risks associated with treatment, and what to do if the patient experiences symptoms that may require emergency care. The form is signed by the patient and the provider and placed in the patient's medical record, and a copy is provided to the patient, to document the patient's acknowledgment of receiving the information from the prescriber. The Agency agrees that the further clarification that signatures can be written or electronic is appropriate for the continued use of the form.

The reference to ectopic pregnancy has been reorganized in the document since it is not a risk of the drug. The signs and symptoms of an untreated ectopic pregnancy that may persist after mifepristone use have been clarified in the section of the form that explains the signs and symptoms of potential problems that may occur after mifepristone use.

The review team agrees with removing the patient's agreement to take the Medication Guide with them if they visit an emergency room or HCP who did not give them mifepristone so the emergency room or HCP will understand that the patient is having a medical abortion. Although this statement has been in the Medication Guide for a number of years, upon further consideration, the Agency has concluded that patients seeking emergency medical care are not likely to carry a Medication Guide with them, the Medication Guide is readily available online, and information about medical conditions and previous treatments can be obtained at the point of care.

3.3.2.3. Pharmacy Requirements

The Sponsors proposed that certified pharmacies, in addition to certified prescribers and HCPs under the supervision of certified prescribers, can dispense mifepristone. In order for a pharmacy to become certified, the pharmacy must designate an authorized representative to carry out the certification process and oversee implementation and compliance with the Mifepristone REMS Program on behalf of the pharmacy. The Authorized Representative must certify that they have read and understood the Prescribing Information for mifepristone. Each location of the pharmacy must be able to receive *Prescriber Agreement Forms* by email and fax and be able to ship mifepristone using a shipping service that provides tracking information.

Additionally, each dispensing pharmacy location must put processes and procedures in place to fulfill the REMS requirements. Certified pharmacies must verify prescriber certification by confirming they have obtained a copy of the prescriber's signed *Prescriber Agreement Form* before dispensing. Certified pharmacies must dispense mifepristone such that it is received by the patient within four days from the day of prescription receipt by the pharmacy. If the pharmacy will not be able to deliver mifepristone to the patient within four days of receipt of the prescription, the pharmacy must contact the prescriber to confirm the appropriateness of dispensing mifepristone and document the certified prescriber's decision. The pharmacy must also record the NDC and lot number from each package of mifepristone dispensed in the patient's record, track and verify receipt of each shipment of mifepristone, dispense mifepristone in its original package, and only distribute, transfer, loan, or sell mifepristone to certified prescribers or between locations of the certified pharmacy. The pharmacy must also report any patient deaths to the prescriber, including the NDC and lot number from the package dispensed to the patient, and remind the prescriber of their obligation under the REMS to report patient deaths to the Sponsor that supplied the mifepristone; the certified pharmacy also must notify the Sponsor that supplied the mifepristone that the pharmacy submitted a report of a patient death to the prescriber and include the name and contact information for the prescriber as well as the NDC and lot number of the dispensed

product. Record-keeping requirements of the pharmacy include records of *Prescriber Agreement Forms*, mifepristone dispensing and shipping, and all processes and procedures and compliance with those processes and procedures. Pharmacies must train all relevant staff and participate in compliance audits. Pharmacies must also maintain the identity of patients and providers as confidential, including limiting access to patient and provider identity only to those personnel necessary to dispense mifepristone in accordance with the Mifepristone REMS Program requirements, or as necessary for payment and/or insurance purposes. The requirement that mifepristone not be dispensed from retail pharmacies was removed.

The following materials support pharmacy requirements:

- *Pharmacy Agreement Form* for Danco Laboratories, LLC
- *Pharmacy Agreement Form* for GenBioPro, Inc.

Reviewer Comment: *We agree with the Sponsors' proposal. The Mifepristone REMS Program continues to require that mifepristone be prescribed only by certified prescribers. With the removal of the in-person dispensing requirement, however, mifepristone can be dispensed from a pharmacy, provided the product is prescribed by a certified prescriber and all other requirements of the REMS are met. Given this modification to the dispensing requirements in the REMS, it is necessary to add a requirement for certification of pharmacies. Adding the pharmacy certification requirement incorporates pharmacies into the REMS, ensures that pharmacies are aware of and agree to follow applicable REMS requirements, and ensures that mifepristone is only dispensed pursuant to prescriptions that are written by certified prescribers. Without pharmacy certification, a pharmacy might dispense product that was not prescribed by a certified prescriber. Adding pharmacy certification ensures that the prescriber is certified prior to dispensing the product to a patient; certified prescribers, in turn, have agreed to meet all the conditions of the REMS, including ensuring that the Patient Agreement Form is completed. In addition, wholesalers and distributors can only ship to certified pharmacies. Based on our review and our consideration of the distribution model implemented by the Sponsors during the periods when the in-person dispensing requirement was not being enforced, as well as REMS assessment data and published literature, we conclude that provided all other requirements of the REMS are met, the REMS program, with the removal of the in-person dispensing requirement and the addition of a requirement for pharmacy certification, will continue to ensure the benefits of mifepristone for medical abortion outweigh the risks while minimizing the burden imposed by the REMS on healthcare providers and patients.*

The requirement to maintain confidentiality, including limiting access to patient and provider identity only to those personnel necessary for dispensing under the Mifepristone REMS Program or as necessary for payment and/or insurance purposes, is included to avoid unduly burdening patient access.

The Sponsors proposed inclusion of this requirement because of concerns that patients may be reluctant or unwilling to seek to obtain mifepristone from pharmacies if they are concerned that confidentiality of their medical information could be compromised, potentially exposing them to intimidation, threats, or acts of violence by individuals opposed to the use of mifepristone for medical abortion.^e Further, unwillingness on the part of prescribers to participate in the Mifepristone REMS Program on the basis of

^e See e.g., 2020 Violence and Disruption Statistics, National Abortion Federation (Dec. 16, 2021), <https://prochoice.org/national-abortion-federation-releases-2020-violence-disruption-statistics/>; Amanda Musa, CNN, *Wyoming Authorities Search for a Suspect Believed to Have Set an Abortion Clinic on Fire*, CNN WIRE (June 10, 2022), <https://abc17news.com/news/2022/06/10/wyoming-authorities-search-for-a-suspect-believed-to-have-set-an-abortion-clinic-on-fire/>.

similar confidentiality concerns may unduly burden patient access by limiting the number of prescribers who are willing to send prescriptions to certified pharmacies. Addition of this requirement protects patient access by requiring the pharmacy to put processes and procedures in place to limit access to confidential information to only those individuals who are essential for dispensing mifepristone under the Mifepristone REMS Program or as necessary for payment or insurance purposes. Inclusion of this requirement for certified pharmacies is consistent with the requirement in the current Mifepristone REMS Program, that distributors maintain secure and confidential records.

Reference to mifepristone not being available in retail pharmacies was removed from the REMS. There is no single definition of the term "retail pharmacy" and therefore the scope of the exclusion in the REMS was not well defined. Including a restriction in the Mifepristone REMS Program that retail pharmacies cannot participate in the REMS may unintentionally prohibit the participation of mail order and specialty pharmacies that could, under one or more definitions, also be considered a "retail pharmacy."

After reconsideration of the term, "retail," the Agency concluded that a more appropriate approach was to articulate the specific requirements that would be necessary for pharmacy certification. As modified, the REMS will not preclude the participation of any pharmacy that meets the certification requirements. However, we acknowledge that the provision in the REMS related to pharmacies' verification of prescriber enrollment will likely limit the types of pharmacies that will choose to certify in the REMS. The REMS requires that pharmacies dispense mifepristone only after verifying that the prescriber is certified. The REMS further requires that pharmacies be able to receive the Prescriber Agreement Forms by email and fax.

(b) (4)

The pharmacy certification requirements include that the drug reach patients within four days of the certified pharmacy receiving the prescription. During the course of the review, the review team concluded that requiring medication delivery to the patient within four days of the pharmacy's receipt of a prescription is acceptable based on the labeled indication and literature,¹³ while taking into account practical shipping considerations (e.g., shipping over weekends and holidays). For patients who will not receive the drug within four calendar days of the date the pharmacy receives the prescription, the pharmacy must notify the certified prescriber and the certified prescriber must determine if it is still appropriate for the certified pharmacy to dispense the drug. The pharmacy must document the certified prescriber's decision. A prescriber's confirmation that it is appropriate to dispense mifepristone when it will not be delivered to the patient within the allotted four days is intended to ensure timeliness of delivery in light of the labeled indication and gestational age.

Pharmacy Agreement Form

The proposed *Pharmacy Agreement Form* is a new form and is the means by which a pharmacy becomes certified to dispense mifepristone. The form, which is submitted by an authorized representative on behalf of a pharmacy seeking certification, outlines all requirements proposed above. Clarification is included in the form that healthcare settings, such as medical offices, clinics, and hospitals, where mifepristone will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program, do not require pharmacy certification. Any new authorized representative must complete and submit the *Pharmacy Agreement Form*. Spaces for specific authorized representative information and pharmacy name and address are included. The completed form can be submitted by email or fax to the authorized distributor.

Reviewer Comment: *We agree with the Sponsors' proposal. The Pharmacy Agreement Form aligns with the pharmacy requirements discussed above.*

3.3.2.4. Distributor Requirements

The Sponsors proposed that the distributors' processes and procedures in the approved Mifepristone REMS Program be updated to ensure that mifepristone is only shipped to clinics, medical offices and hospitals identified by certified prescribers and to certified pharmacies. Distributors will continue to complete the certification process for any *Prescriber Agreement Forms* they receive and also will complete the certification process for pharmacies upon receipt of a *Pharmacy Agreement Form*, including notifying pharmacies when they become certified. FDA was removed as a potential auditor for distributors.

Reviewer Comment: *We agree with the Sponsors' proposal. At this time, FDA does not audit distributors directly, it carries out inspections of Sponsors to monitor industry compliance with REMS requirements.*

3.3.3. REMS Sponsor Requirements

3.3.3.1. Sponsor Requirements to Support Prescriber Certification

The Sponsors proposed additions to this section of the REMS document, including that Sponsors will ensure prescribers can complete the certification process by email or fax to an authorized distributor and/or certified pharmacy, and that Sponsors will ensure annually with each certified prescriber that their locations for receiving mifepristone are up to date. Sponsors will also ensure prescribers previously certified in the Mifepristone REMS Program complete the new *Prescriber Agreement Form*: (1) within 120 days after approval of this modification, for those previously certified prescribers submitting prescriptions to certified pharmacies, or (2) within one year after approval of this modification, if previously certified and ordering from an authorized distributor.

Reviewer Comment: *We agree with the Sponsors' proposal. The requirement to confirm that the locations associated with the certified prescriber are current is parallel to the pharmacy requirement that the authorized representative's contact information is up to date. In determining the pharmacy requirement, which is necessary to ensure program compliance and is consistent with other approved REMS that include pharmacy certification, the Agency also concluded that a parallel requirement for certified prescribers should be added.*

With respect to recertification, it is important that active certified prescribers are informed of and agree to new REMS requirements to ensure the continued safe use of mifepristone. There is minimal burden to recertification and the timelines allow sufficient time to accomplish recertification.

3.3.3.2. Sponsor Requirements to Support Pharmacy Certification

The Sponsors proposed the addition of Sponsor requirements to support pharmacy certification and compliance, including ensuring that pharmacies are certified in accordance with the requirements in the Mifepristone REMS Program, de-certifying pharmacies that do not maintain compliance with the certification requirements, and ensuring that pharmacy certification can be completed by email and fax to an authorized distributor. Annually, the authorized representative's name and contact information will be verified to ensure it corresponds to that of the current designated authorized representative for the certified pharmacy, and if different, a new authorized representative must certify for the pharmacy. All reference to the requirement in the 2021 Mifepristone REMS Program that mifepristone to be dispensed to patients only in clinics, medical offices and hospitals by or under the supervision of a certified prescriber, and not from retail pharmacies, was removed.

Reviewer Comment: *We agree with the Sponsors' proposal. Changes are in line with the REMS Modification Notification letters sent December 16, 2021. Refer to section 3.3.2.3 Reviewer Comments on Pharmacy Certification for rationale for removing the statement that mifepristone is not distributed to or dispensed from retail pharmacies. Ensuring that the authorized representative's contact information is up to date is necessary to ensure that there is always a point person who is responsible for implementing the Mifepristone REMS Program in their pharmacy and can address any changes that are needed if pharmacy audits identify a need for improvement.*

3.3.3.3. Sponsor Implementation Requirements

The Sponsors proposed that they will ensure that adequate records are maintained to demonstrate that REMS requirements have been met (including but not limited to records of mifepristone distribution, certification of prescribers and pharmacies, and audits of pharmacies and distributors), and that the records must be readily available for FDA inspections. The distributor audit requirement was updated to audit new distributors within 90 calendar days of becoming authorized and annually thereafter (a one-time audit requirement was previously required). The Sponsors also proposed a pharmacy audit requirement whereby certified pharmacies that order mifepristone are audited within 180 calendar days after the pharmacy places its first order of mifepristone, and annually thereafter for pharmacies that ordered in the previous 12 months.

Reviewer's Comment: *We agree with the Sponsors' proposal.*

The number of pharmacies that will certify in the REMS is uncertain; therefore, to obtain a reliable sample size for the audits, the Sponsors will need to audit all certified pharmacies within 180 calendar days after the pharmacy places its first order and annually thereafter for pharmacies that have ordered mifepristone in the previous 12 months. Audits performed at 180 days should allow time for establishment and implementation of audit protocols and for the Sponsors to perform the audits. With the addition of more stakeholders (i.e., certified pharmacies), it is also necessary to audit distributors annually to ensure the REMS requirements are followed. The requirement to conduct audits annually may be revisited if assessment data shows that the REMS is meeting its goal.

3.4. REMS Assessment Timetable

The Sponsors proposed that assessments must be submitted one year from the approval of the modified REMS and annually thereafter, instead of every three years as per the previous requirement.

Reviewer's Comment: *We agree with the Sponsors' proposal. With the addition of new pharmacy stakeholders and removal of the in-person dispensing requirement, more frequent assessment after this REMS modification is needed to ensure REMS processes are being followed and that the REMS is meeting its goal. The requirement can be revisited at a later date if assessment data shows that the modified REMS is meeting its goal. The NDA applicant is required to submit assessment reports as outlined in the timetable for submission of assessments. These reports address requirements for the Mifepristone REMS Program. The Sponsors have indicated that some data will be submitted as separate reports when Sponsor-specific information is needed to address the assessment metrics.*

4. Supporting Document

The Sponsors' REMS Supporting Document was substantially updated to include information regarding the proposed modification under review. Background and rationale from the 12/16/21 REMS Modification Notification letters was included. An updated description of the REMS goal and the ETASU was also included to align with the changes in the REMS Document and provide further clarification. Further explanation of prescriber requirements and rationale for various pharmacy requirements was also included.

Regarding implementation of the modified REMS, the Sponsors additionally proposed that pharmacies that received and shipped mifepristone during the Agency's exercise of enforcement discretion during the COVID-19 PHE, that wish to continue to dispense mifepristone, will be required to comply with the pharmacy certification requirements within 120 days of approval of the modified REMS.

The communication strategy to alert current and future prescriber and pharmacy stakeholders was outlined. Distributors, certified prescribers that purchased mifepristone in the last twelve months, and various professional organizations will receive information about REMS changes within 120 days of modification approval. The Sponsors proposed to list pharmacies that agree to be publicly disclosed on their respective product websites but disclosure of this nature is not a requirement of the REMS. The Sponsors indicated that they anticipate certified pharmacies that do not agree to public disclosure will communicate with the certified prescribers they wish to work with.

The REMS Assessment Plan is discussed in the following section.

Reviewer's Comment: *We agree with the Sponsors' proposal. The Supporting Document addresses all REMS requirements and provides sufficient clarification of implementation and maintenance of the REMS. The implementation requirements for pharmacies currently dispensing mifepristone under FDA's exercise of enforcement discretion during the COVID-19 PHE provide for continued use of these pharmacies without breaks in service. The communication strategy is also adequate given the efforts to reach both established certified prescribers and potentially new prescribers through professional organizations.*

The Sponsors' plan to communicate which pharmacies are certified to certified prescribers is adequate. For the reasons listed in section 3.3.2.3, confidentiality is a concern for REMS stakeholders. Disclosure of pharmacy certification status should be a choice made by individual certified pharmacies. The Sponsors have indicated that there will be some certified pharmacies that have agreed to publicly disclose their status, making this information available to certified prescribers who wish to use a pharmacy to dispense mifepristone.

5. REMS Assessment Plan

The REMS Assessment Plan is summarized in the REMS Supporting Document and will be included in the REMS Modification Approval letter.

The REMS Assessment Plan was revised to align with the modified REMS goal and objectives.

The goal of the Mifepristone REMS Program is to mitigate the risk of serious complications associated with mifepristone by:

- a. Requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program.
 - This objective will be assessed using REMS Certification Statistics and REMS Compliance metrics.
- b. Ensuring that mifepristone is only dispensed by or under the supervision of certified prescribers, or by certified pharmacies on prescriptions issued by certified prescribers.
 - This objective will be assessed using REMS Certification Statistics and REMS Compliance metrics.
- c. Informing patients about the risk of serious complications associated with mifepristone.
 - This objective will be indirectly assessed using REMS Certification Statistics to avoid compromising patient and prescriber confidentiality. As part of the certification process, healthcare providers agree to:
 - Ensure that the *Patient Agreement Form* is reviewed with the patient and the risks of the mifepristone treatment regimen are fully explained
 - Ensure that the *Patient Agreement Form* is signed by the healthcare provider and the patient
 - Ensure that the patient is provided with a copy of the *Patient Agreement Form* and the Medication Guide
 - Ensure that the signed *Patient Agreement Form* is placed in the patient's medical record

The following revisions were made from the Mifepristone REMS Assessment Plan in the April 11, 2019, Supplement Approval letter:

The Assessment Plan Categories of 1) Program Implementation and Operations and 2) Overall Assessment of REMS Effectiveness were added.

REMS Certification Statistics metrics were added to capture certification numbers for program stakeholders to assess the first objective of requiring healthcare providers who prescribe mifepristone to be certified and the second objective of ensuring that mifepristone is only dispensed by or under the supervision of certified prescribers, or by certified pharmacies on prescriptions issued by certified prescribers. The total number of certified prescribers who certified with the wholesaler/distributor and the total number of certified prescribers who submitted a *Prescriber Agreement Form* to certified pharmacies were added to capture the additional method of prescriber certification. The number of newly certified prescribers and the number of active certified prescribers (i.e., those who ordered mifepristone or submitted a prescription during the reporting period) were added. Metrics were also added to capture the total number of certified, newly certified, and active certified pharmacies as well as the total number of authorized, newly authorized, and active authorized wholesaler/distributors.

Drug Utilization Data metrics were added to obtain information on shipment and dispensing of mifepristone. Metrics were added to capture the total number of tablets shipped by the wholesaler/distributor and the number of prescriptions dispensed.

REMS Compliance Data metrics were added to assess the first objective of requiring healthcare providers who prescribe mifepristone to be certified and the second objective of ensuring that mifepristone is only dispensed by or under the supervision of certified prescribers, or by certified pharmacies on prescriptions issued by certified prescribers. These metrics capture program deviations and evaluate overall if the REMS is operating as intended. Metrics include certified pharmacies and wholesaler/distributor audit results and a summary of instances of non-compliance and actions taken to address non-compliance. Prescriber compliance metrics were added to assess if prescribers are decertified along with reasons why. Pharmacy compliance metrics were added to assess if prescriptions were dispensed that were written by non-certified prescribers or if mifepristone tablets were dispensed by non-certified pharmacies as well as the number of pharmacies that were decertified along with reasons why. Wholesaler/distributor metrics were added to assess if shipments were sent to non-certified prescribers and non-certified pharmacies and corrective actions taken. The audit plan and non-compliance plans will be submitted for FDA review within 60 days after the REMS modification approval.

The Sponsors were asked to develop an assessment of prescription delivery timelines to determine what percentage of prescriptions were delivered on time (within four calendar days) and what percentage were delivered late (more than four calendar days) along with the length of the delay and reasons for the delay (e.g., mifepristone is out of stock shipment issues, other). The protocol for this assessment will be submitted for FDA review within 60 days after the REMS modification approval.

The revised REMS Assessment Plan is in the Appendix.

Reviewer's Comment: *We agree with the Sponsors' proposed REMS Assessment Plan.*

6. Discussion

The Sponsors submitted changes to the REMS to remove the requirement that mifepristone be dispensed only in certain healthcare settings (i.e., the "in-person dispensing requirement") and to add that certified pharmacies can dispense the drug in order to minimize the burden on the healthcare delivery system of complying with the REMS and to ensure that the benefits of the drug outweigh the risks. The REMS goal was updated to this effect. Changes were required for prescriber requirements and Sponsors to support the change in ETASU, and new pharmacy requirements were introduced.

The qualifications to become a certified prescriber have not changed as a result of the modification to the Mifepristone REMS Program; however, clarification has been provided for certain prescriber requirements and new prescriber requirements have been added to support pharmacy dispensing. Although certain responsibilities may be conducted by staff under the supervision of a certified prescriber, the certified prescriber remains responsible for ensuring compliance with the requirements of the Mifepristone REMS Program. In order to clarify this, revisions were made throughout the prescriber requirements and REMS materials to reflect that the certified prescriber is responsible for ensuring that the prescriber requirements are met. Additionally, the review team finds it acceptable that certified prescribers who wish to use a certified pharmacy to dispense mifepristone submit their *Prescriber Agreement Form* to the dispensing certified pharmacy (b) (4).

. The burden to prescriber and

pharmacy stakeholders of having certified prescribers submit the form directly to the certified pharmacy that will be dispensing the mifepristone is not unreasonable and has been minimized to the extent possible; it does not impact the safe use of the product. Prescriber requirements necessitated by the addition of some pharmacy requirements were added as well and include prescriber responsibilities in deciding whether or not mifepristone should be dispensed if the patient will receive the drug from the certified pharmacy more than four days after the pharmacy receives the prescription, and prescriber adverse event reporting requirements if a prescriber becomes aware of a patient death and the mifepristone was dispensed from a certified pharmacy. The addition of the latter requirements will ensure consistent adverse event data is relayed to the relevant Mifepristone Sponsor.

Changes were made to the *Patient Agreement Form*. Changes to the form were added to improve clarity of the safety messages. After further consideration, the patient's agreement to take the Medication Guide with them if they visit an emergency room or HCP who did not give them mifepristone so the emergency room or HCP will understand that the patient is having a medical abortion has been removed from the *Patient Agreement Form*. The Medication Guide is not typically carried by patients and this information can be obtained at the point of care. Changes align with updates to labeling submitted with this modification.^{13, 14}

The Agency and Sponsors agreed during this modification to focus on certification of pharmacies that can receive *Prescriber Agreement Forms* via email or fax to complete the prescriber certification process. The proposed pharmacy certification requirements also support timely dispensing of mifepristone. If the mifepristone is shipped to the patient, the REMS requires that it must be delivered within four calendar days from the receipt of the prescription by the pharmacy; if the patient will receive the mifepristone more than four calendar days from pharmacy receipt of prescription, the REMS requires the pharmacist to confirm with the certified prescriber that it is still appropriate to dispense the drug to the patient. This allows prescribers to make treatment decisions based on individual patient situations. A requirement to maintain confidentiality was also added to avoid unduly burdening patient access since patients and prescribers may not utilize pharmacy dispensing if they believe their personal information is at risk. Ultimately, the addition of pharmacy distribution with the proposed requirements will offer another option for dispensing mifepristone, alleviating burden associated with the REMS.

(b) (4)

The Agency reviewed the REMS in 2021, and per the review team's conclusions, a REMS modification was necessary to remove the in-person dispensing requirement and add a requirement that pharmacies that dispense the drug be specially certified; the review team concluded that these changes could occur without compromising patient safety. There have been no new safety concerns identified relevant to the REMS ETASUs that the applicants proposed modifying in their June 22, 2022 submissions since the REMS Modification Notification letters dated 12/16/2021. It is still the position of the review team that the proposed modification is acceptable.

Because the modification proposed include changes to the ETASU of the Mifepristone REMS Program, the assessment plan and timetable of assessments were changed. The assessment plan will capture information on pharmacy dispensing and provide valuable insight as to whether the program is operating as intended. Annual assessments are consistent with other approved REMS modifications for major modifications necessitating extensive assessment plan changes.

As part of the REMS Assessment Plan, the REMS goal and objectives are assessed using Program Implementation and Operations Metrics, including REMS Certification Statistics and REMS Compliance Data. The metrics will provide information on the number of certified prescribers, certified pharmacies, and authorized wholesalers/distributors as well as if mifepristone is dispensed by non-certified prescribers or pharmacies. The Sponsors will use the indirect measure of healthcare provider certification to address the objective of informing patients of the risk of serious complications of mifepristone, due to concerns with prescriber and patient confidentiality. Although we typically assess whether patients are informed of the risks identified in a REMS through patient surveys and/or focus groups, we agree that the Sponsors' continued use of the indirect measure of healthcare provider certification adequately addresses the Mifepristone REMS Program objective of informing patients. In addition, because of these prescriber and patient confidentiality concerns, we believe it is unlikely that the Agency would be able to use the typical methods of assessment of patient knowledge and understanding of the risks and safe use of mifepristone.

7. Conclusions and Recommendations

The review team finds the proposed REMS modification for the Mifepristone REMS Program, as submitted on June 22, 2022, and amended on October 19, 2022 (Danco) and October 20, 2022 (GBP), November 30, 2022 (both), December 9 (both), and December 16 (both) acceptable. The REMS materials were amended to be consistent with the revised REMS document. The review team recommends approval of the Mifepristone REMS Program, received on June 22, 2022, and last amended on December 16, 2022, and appended to this review.

8. References

1. (b) (6) Clinical Review of SE-2 Efficacy Supplement for mifepristone, NDA 020687. March 29, 2016. DARRTS Reference ID: 3909590.
2. (b) (6) Summary Review for Regulatory Action for mifepristone, NDA 020687. March 29, 2016. DARRTS Reference ID: 3909594.
3. (b) (6) REMS Review for mifepristone, NDA 020687. March 29, 2016. DARRTS Reference ID: 3909588.
4. (b) (6) REMS Review for mifepristone, NDA 020687. March 29, 2016. DARRTS Reference ID: 3909587.
5. Approval Letter for SE-2 Efficacy Supplement for mifepristone, NDA 020687. March 29, 2016. DARRTS Reference ID: 3909592.
6. (b) (6) REMS Review for mifepristone, NDA 020687. February 22, 2018. DARRTS Reference ID: 4224674.
7. Approval Letter for SE-20 REMS Supplement for mifepristone, NDA 020687. March 29, 2016. DARRTS Reference ID: 4418041.
8. *Am. Coll. of Obstetricians & Gynecologists v. FDA*, 472 F. Supp. 3d 183, 233 (D. Md. July 13, 2020), order clarified, 2020 WL 8167535 (D. Md. Aug. 19, 2020) (preliminarily enjoining FDA from enforcing the in-person dispensing requirement and any other in-person requirements of the

Mifepristone SSS REMS); *FDA v. Am. Coll. of Obstetricians & Gynecologists*, 141 S. Ct. 578 (Jan. 12, 2021) (staying the preliminary injunction imposed by the District Court).

9. (b) (6) REMS Modification Rationale Review for mifepristone, NDA 020687. December 16, 2021. DARRTS Reference ID: 4905882.

10. General Advice Letter for the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone, NDA 020687, April 15, 2022. DARRTS ID 4969358.

11. Format and Content of a REMS Document Guidance for Industry <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf>. Accessed on December 18, 2022.

12. Grossman D, Raifman S, Morris N, et.al. Mail-order pharmacy dispensing of mifepristone for medication abortion after in-person clinical assessment. *Contraception* 2022; 107:36-41. <https://doi.org/10.1016/j.contraception.2021.09.008>. This article was included in the literature review for the December 16, 2021 REMS Modification Rationale Review, while the article was still in press.

9. Appendices

REMS Document

Prescriber Agreement Form for Danco Laboratories, LLC

Prescriber Agreement Form for GenBioPro, Inc.

Patient Agreement Form

Pharmacy Agreement Form for Danco Laboratories, LLC

Pharmacy Agreement Form for GenBioPro, Inc.

Mifepristone REMS Assessment Plan

Initial Shared System REMS approval: 04/2019

Most Recent Modification: 01/2023

Mifepristone Tablets, 200 mg

Progestin Antagonist

**RISK EVALUATION AND MITIGATION STRATEGY (REMS)
SINGLE SHARED SYSTEM FOR MIFEPRISTONE 200 MG**

I. GOAL

The goal of the REMS for mifepristone is to mitigate the risk of serious complications associated with mifepristone by:

- a) Requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program.
- b) Ensuring that mifepristone is only dispensed by or under the supervision of certified prescribers, or by certified pharmacies on prescriptions issued by certified prescribers.
- c) Informing patients about the risk of serious complications associated with mifepristone.

II. REMS ELEMENTS

A. Elements to Assure Safe Use

1. Healthcare providers who prescribe mifepristone must be specially certified.
 - a. To become specially certified to prescribe mifepristone, healthcare providers must:
 - i. Review the Prescribing Information for mifepristone.
 - ii. Complete a *Prescriber Agreement Form*. By signing¹ a *Prescriber Agreement Form*, prescribers agree that:
 - 1) They have the following qualifications:
 - a) Ability to assess the duration of pregnancy accurately
 - b) Ability to diagnose ectopic pregnancies
 - c) Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or to have made plans to provide such care through others, and ability to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary
 - 2) They will follow the guidelines for use of mifepristone (see b.i-vii below).
 - b. As a condition of certification, prescribers must follow the guidelines for use of mifepristone described below:
 - i. Ensure that the *Patient Agreement Form* is reviewed with the patient and the risks of the mifepristone treatment regimen are fully explained. Ensure any questions the patient may have prior to receiving mifepristone are answered.
 - ii. Ensure that the healthcare provider and patient sign the *Patient Agreement Form*.

¹ In this REMS, the terms “sign” and “signature” include electronic signatures.

- iii. Ensure that the patient is provided with a copy of the *Patient Agreement Form* and Medication Guide.
 - iv. Ensure that the signed *Patient Agreement Form* is placed in the patient's medical record.
 - v. Ensure that any deaths are reported to the Mifepristone Sponsor that provided the mifepristone, identifying the patient by a non-identifiable reference and including the NDC and lot number from the package of mifepristone that was dispensed to the patient.
 - vi. If mifepristone will be dispensed by a certified pharmacy:
 - 1) Provide the certified pharmacy a signed *Prescriber Agreement Form*.
 - 2) Assess appropriateness of dispensing mifepristone when contacted by a certified pharmacy about patients who will receive mifepristone more than 4 calendar days after the prescription was received by the certified pharmacy.
 - 3) Obtain the NDC and lot number of the package of mifepristone the patient received in the event the prescriber becomes aware of the death of the patient.
 - vii. The certified prescriber who dispenses mifepristone or who supervises the dispensing of mifepristone must:
 - 1) Provide an authorized distributor with a signed *Prescriber Agreement Form*.
 - 2) Ensure that the NDC and lot number from each package of mifepristone dispensed are recorded in the patient's record.
 - 3) Ensure that healthcare providers under their supervision follow guidelines i.-v.
 - c. Mifepristone Sponsors must:
 - i. Ensure that healthcare providers who prescribe their mifepristone are specially certified in accordance with the requirements described above and de-certify healthcare providers who do not maintain compliance with certification requirements.
 - ii. Ensure prescribers previously certified in the Mifepristone REMS Program complete the new *Prescriber Agreement Form*:
 - 1) Within 120 days after approval of this modification, for those previously certified prescribers submitting prescriptions to certified pharmacies.
 - 2) Within one year after approval of this modification, if previously certified and ordering from an authorized distributor.
 - iii. Ensure that healthcare providers can complete the certification process by email or fax to an authorized distributor and/or certified pharmacy.
 - iv. Provide the Prescribing Information and their *Prescriber Agreement Form* to healthcare providers who inquire about how to become certified.
 - v. Ensure annually with each certified prescriber that their locations for receiving mifepristone are up to date.
- The following materials are part of the Mifepristone REMS Program:
- *Prescriber Agreement Form for Danco Laboratories, LLC*
 - *Prescriber Agreement Form for GenBioPro, Inc.*
 - *Patient Agreement Form*

2. Pharmacies that dispense mifepristone must be specially certified
 - a. To become specially certified to dispense mifepristone, pharmacies must:
 - i. Be able to receive *Prescriber Agreement Forms* by email and fax.
 - ii. Be able to ship mifepristone using a shipping service that provides tracking information.
 - iii. Designate an authorized representative to carry out the certification process on behalf of the pharmacy.
 - iv. Ensure the authorized representative oversees implementation and compliance with the Mifepristone REMS Program by doing the following:
 - 1) Review the Prescribing Information for mifepristone.
 - 2) Complete a *Pharmacy Agreement Form*. By signing a *Pharmacy Agreement Form*, the authorized representative agrees that the pharmacy will put processes and procedures in place to ensure the following requirements are completed:
 - a) Verify that the prescriber is certified by confirming their completed *Prescriber Agreement Form* was received with the prescription or is on file with the pharmacy.
 - b) Dispense mifepristone such that it is delivered to the patient within 4 calendar days of the date the pharmacy receives the prescription, except as provided in c) below.
 - c) Confirm with the prescriber the appropriateness of dispensing mifepristone for patients who will receive the drug more than 4 calendar days after the date the pharmacy receives the prescription and document the prescriber's decision.
 - d) Record in the patient's record the NDC and lot number from each package of mifepristone dispensed.
 - e) Track and verify receipt of each shipment of mifepristone.
 - f) Dispense mifepristone in its package as supplied by the Mifepristone Sponsor.
 - g) Report any patient deaths to the prescriber, including the NDC and lot number from the package of mifepristone dispensed to the patient, and remind the prescriber of their obligation to report the deaths to the Mifepristone Sponsor that provided the mifepristone. Notify the Mifepristone Sponsor that provided the dispensed mifepristone that the pharmacy submitted a report of death to the prescriber, including the name and contact information for the prescriber and the NDC and lot number of the dispensed product.
 - h) Not distribute, transfer, loan or sell mifepristone except to certified prescribers or other locations of the pharmacy.
 - i) Maintain records of *Prescriber Agreement Forms*.
 - j) Maintain records of dispensing and shipping.
 - k) Maintain records of all processes and procedures including compliance with those processes and procedures.
 - l) Maintain the identity of the patient and prescriber as confidential, including limiting access to patient and prescriber identity only to those personnel necessary to dispense mifepristone in accordance with the Mifepristone REMS Program requirements, or as necessary for payment and/or insurance purposes.
 - m) Train all relevant staff on the Mifepristone REMS Program requirements.

- n) Comply with audits carried out by the Mifepristone Sponsors or a third party acting on behalf of the Mifepristone Sponsors to ensure that all processes and procedures are in place and are being followed.
- b. Mifepristone Sponsors must:
 - i. Ensure that pharmacies are specially certified in accordance with the requirements described above and de-certify pharmacies that do not maintain compliance with certification requirements.
 - ii. Ensure that pharmacies can complete the certification process by email and fax to an authorized distributor.
 - i. Verify annually that the name and contact information for the pharmacy's authorized representative corresponds to that of the current designated authorized representative for the certified pharmacy, and if different, require the pharmacy to recertify with the new authorized representative.

The following materials are part of the Mifepristone REMS Program:

- *Pharmacy Agreement Form for Danco Laboratories, LLC*
- *Pharmacy Agreement Form for GenBioPro, Inc.*
- 3. Mifepristone must be dispensed to patients with evidence or other documentation of safe use conditions as ensured by the certified prescriber in signing the *Prescriber Agreement Form*.
 - a. The patient must sign a *Patient Agreement Form* indicating that the patient has:
 - i. Received, read and been provided a copy of the *Patient Agreement Form*.
 - ii. Received counseling from the healthcare provider regarding the risk of serious complications associated with mifepristone.

B. Implementation System

- 1. Mifepristone Sponsors must ensure that their mifepristone is only distributed to certified prescribers and certified pharmacies by:
 - a. Ensuring that distributors who distribute their mifepristone comply with the program requirements for distributors.
 - i. The distributors must put processes and procedures in place to:
 - 1) Complete the certification process upon receipt of a *Prescriber Agreement Form* or *Pharmacy Agreement Form*.
 - 2) Notify healthcare providers and pharmacies when they have been certified by the Mifepristone REMS Program.
 - 3) Ship mifepristone only to certified pharmacies or locations identified by certified prescribers.
 - 4) Not ship mifepristone to pharmacies or prescribers who become de-certified from the Mifepristone REMS Program.
 - 5) Provide the Prescribing Information and their Prescriber Agreement Form to healthcare providers who (1) attempt to order mifepristone and are not yet certified, or (2) inquire about how to become certified.
 - ii. Put processes and procedures in place to maintain a distribution system that is secure,

confidential and follows all processes and procedures, including those for storage, handling, shipping, tracking package serial numbers, NDC and lot numbers, proof of delivery and controlled returns of mifepristone.

- iii. Train all relevant staff on the Mifepristone REMS Program requirements.
 - iv. Comply with audits by Mifepristone Sponsors or a third party acting on behalf of Mifepristone Sponsors to ensure that all processes and procedures are in place and are being followed for the Mifepristone REMS Program. In addition, distributors must maintain appropriate documentation and make it available for audits.
- b. Ensuring that distributors maintain secure and confidential distribution records of all shipments of mifepristone.
- 2. Mifepristone Sponsors must monitor their distribution data to ensure compliance with the Mifepristone REMS Program.
- 3. Mifepristone Sponsors must ensure that adequate records are maintained to demonstrate that the Mifepristone REMS Program requirements have been met, including, but not limited to records of mifepristone distribution; certification of prescribers and pharmacies; and audits of pharmacies and distributors. These records must be readily available for FDA inspections.
- 4. Mifepristone Sponsors must audit their new distributors within 90 calendar days and annually thereafter after the distributor is authorized to ensure that all processes and procedures are in place and functioning to support the requirements of the Mifepristone REMS Program. Mifepristone Sponsors will take steps to address their distributor compliance if noncompliance is identified.
- 5. Mifepristone Sponsors must audit their certified pharmacies within 180 calendar days after the pharmacy places its first order of mifepristone, and annually thereafter audit certified pharmacies that have ordered mifepristone in the previous 12 months, to ensure that all processes and procedures are in place and functioning to support the requirements of the Mifepristone REMS Program. Mifepristone Sponsors will take steps to address their pharmacy compliance if noncompliance is identified.
- 6. Mifepristone Sponsors must take reasonable steps to improve implementation of and compliance with the requirements of the Mifepristone REMS Program based on monitoring and assessment of the Mifepristone REMS Program.
- 7. Mifepristone Sponsors must report to FDA any death associated with mifepristone whether or not considered drug-related, as soon as possible but no later than 15 calendar days from the initial receipt of the information by the Mifepristone Sponsor. This requirement does not affect the sponsors' other reporting and follow-up requirements under FDA regulations.

C. Timetable for Submission of Assessments

The NDA Sponsor must submit REMS assessments to FDA one year from the date of the approval of the modified REMS (1/3/2023) and annually thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 90 calendar days before the submission date for that assessment. The NDA Sponsor must submit each assessment so that it will be received by the FDA on or before the due date.

MIFEPREX® (Mifepristone) Tablets, 200 mg**PRESCRIBER AGREEMENT FORM**

Mifeprex* (Mifepristone) Tablets, 200 mg, is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation. Please see Prescribing Information and Medication Guide for complete safety information.

To **become a certified prescriber**, you must:

- **If you submit Mifeprex prescriptions for dispensing from certified pharmacies:**
 - Submit this form to each certified pharmacy to which you intend to submit Mifeprex prescriptions. The form must be received by the certified pharmacy before any prescriptions are dispensed by that pharmacy.
- **If you order Mifeprex for dispensing by you or healthcare providers under your supervision:**
 - Submit this form to the distributor. This form must be received by the distributor before the first order will be shipped to the healthcare setting.
 - Healthcare settings, such as medical offices, clinics, and hospitals, where Mifeprex will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification.

Prescriber Agreement: By signing this form, you agree that you meet the qualifications below and will follow the guidelines for use. You are responsible for overseeing implementation and compliance with the Mifepristone REMS Program. You also understand that if the guidelines below are not followed, the distributor may stop shipping mifepristone to the locations that you identify and certified pharmacies may stop accepting your mifepristone prescriptions.

Mifepristone must be provided by or under the supervision of a certified prescriber who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and be able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the Prescribing Information for mifepristone. The Prescribing Information is available by calling 1-877-4 EARLY OPTION (1-877-432-7596 toll-free), or by visiting www.earlyoptionpill.com.

In addition to meeting these qualifications, you also agree to follow these guidelines for use:

- Ensure that the *Patient Agreement Form* is reviewed with the patient and the risks of the mifepristone treatment regimen are fully explained. Ensure any questions the patient may have prior to receiving mifepristone are answered.
- Ensure the healthcare provider and patient sign the *Patient Agreement Form*.
- Ensure that the patient is provided with a copy of the *Patient Agreement Form* and Medication Guide.
- Ensure that the signed *Patient Agreement Form* is placed in the patient's medical record.
- Ensure that any deaths of patients who received Mifeprex are reported to Danco Laboratories, LLC, identifying the patient by a non-identifiable reference and including the NDC and lot number from the package of Mifeprex that was dispensed to the patient.



*MIFEPREX is a registered trademark of Danco Laboratories, LLC
P.O. Box 4816-New York, NY 10185

1-877-4-EARLY-OPTION (1-877-432-7596) www.earlyoptionpill.com

Ensure that healthcare providers under your supervision follow the guidelines listed above.

- If Mifeprex will be dispensed through a certified pharmacy:
 - Assess appropriateness of dispensing Mifeprex when contacted by a certified pharmacy about patients who will receive Mifeprex more than 4 calendar days after the prescription was received by the certified pharmacy.
 - Obtain the NDC and lot number of the package of Mifeprex the patient received in the event the prescriber becomes aware of the death of a patient.
- If Mifeprex will be dispensed by you or by healthcare providers under your supervision:
 - Ensure the NDC and lot number from each package of Mifeprex are recorded in the patient's record.

I understand that a certified pharmacy may dispense mifepristone made by a different manufacturer than that stated on this Prescriber Agreement Form.

Print Name: _____ Title: _____

Signature: _____ Date: _____

Medical License # _____ State _____

NPI # _____

Practice Setting Address: _____

Return completed form to Mifeprex@dancodistributor.com or fax to 1-866-227-3343.

Approved 01/2023 [Doc control ID]



*MIFEPREX is a registered trademark of Danco Laboratories, LLC
P.O. Box 4816-New York, NY 10185
1-877-4-EARLY-OPTION (1-877-432-7596) www.earlyoptionpill.com

PRESCRIBER AGREEMENT FORM

Mifepristone Tablets, 200 mg

Mifepristone Tablets, 200 mg, is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation. Please see Prescribing Information and Medication Guide for complete safety information.

To **become a certified prescriber**, you must:

- **If you submit mifepristone prescriptions for dispensing from certified pharmacies:**
 - Submit this form to each certified pharmacy to which you intend to submit mifepristone prescriptions. The form must be received by the certified pharmacy before any prescriptions are dispensed by that pharmacy.
- **If you order mifepristone for dispensing by you or healthcare providers under your supervision:**
 - Submit this form to the distributor. This form must be received by the distributor before the first order will be shipped to the healthcare setting.
 - Healthcare settings, such as medical offices, clinics, and hospitals, where mifepristone will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification.

Prescriber Agreement: By signing this form, you agree that you meet the qualifications below and will follow the guidelines for use. You are responsible for overseeing implementation and compliance with the Mifepristone REMS Program. You also understand that if the guidelines below are not followed, the distributor may stop shipping mifepristone to the locations that you identify and certified pharmacies may stop accepting your mifepristone prescriptions.

Mifepristone must be provided by or under the supervision of a certified prescriber who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and be able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the Prescribing Information for mifepristone. The Prescribing Information is available by calling 1-855-MIFE-INFO (1-855-643-3463 toll-free), or by visiting www.MifeInfo.com.

In addition to meeting these qualifications, you also agree to follow these guidelines for use:

- Ensure that the *Patient Agreement Form* is reviewed with the patient and the risks of the mifepristone treatment regimen are fully explained. Ensure any questions the patient may have prior to receiving mifepristone are answered.
- Ensure the healthcare provider and patient sign the *Patient Agreement Form*.
- Ensure that the patient is provided with a copy of the *Patient Agreement Form* and Medication Guide.
- Ensure that the signed *Patient Agreement Form* is placed in the patient's medical record.
- Ensure that any deaths of patients who received mifepristone are reported to GenBioPro, Inc. that provided the mifepristone, identifying the patient by a non-identifiable reference and including the NDC and lot number from the package of mifepristone that was dispensed to the patient.

Ensure that healthcare providers under your supervision follow the guidelines listed above.



GenBioPro Inc. - PO Box 32011 - Las Vegas, NV 89103
1-855-MIFE-INFO (1-855-643-3463) - www.MifeInfo.com

- If mifepristone will be dispensed through a certified pharmacy:
 - Assess appropriateness of dispensing mifepristone when contacted by a certified pharmacy about patients who will receive mifepristone more than 4 calendar days after the prescription was received by the certified pharmacy.
 - Obtain the NDC and lot number of the package of mifepristone the patient received in the event the prescriber becomes aware of the death of a patient.
- If mifepristone will be dispensed by you or by healthcare providers under your supervision:
 - Ensure the NDC and lot number from each package of mifepristone are recorded in the patient's record.

I understand that a certified pharmacy may dispense mifepristone made by a different manufacturer than that stated on this Prescriber Agreement Form.

Print Name: _____ Title: _____

Signature: _____ Date: _____

Medical License # _____ State _____

NPI # _____

Practice Setting Address: _____

Return completed form to RxAgreements@GenBioPro.com or fax to 1-877-239-8036

Approved 01/2023 [Doc control ID]



GenBioPro Inc. - PO Box 32011 - Las Vegas, NV 89103
1-855-MIFE-INFO (1-855-643-3463) - www.MifeInfo.com

PATIENT AGREEMENT FORM

Mifepristone Tablets, 200 mg

Healthcare Providers: *Counsel the patient on the risks of mifepristone. Both you and the patient must provide a written or electronic signature on this form.*

Patient Agreement:

1. I have decided to take mifepristone and misoprostol to end my pregnancy and will follow my healthcare provider's advice about when to take each drug and what to do in an emergency.
2. I understand:
 - a. I will take mifepristone on Day 1.
 - b. I will take the misoprostol tablets 24 to 48 hours after I take mifepristone.
3. My healthcare provider has talked with me about the risks, including:
 - heavy bleeding
 - infection
4. I will contact the clinic/office/provider right away if in the days after treatment I have:
 - a fever of 100.4°F or higher that lasts for more than four hours
 - heavy bleeding (soaking through two thick full-size sanitary pads per hour for two hours in a row)
 - severe stomach area (abdominal) pain or discomfort, or I am "feeling sick," including weakness, nausea, vomiting, or diarrhea, more than 24 hours after taking misoprostol
— these symptoms may be a sign of a serious infection or another problem (including an ectopic pregnancy, a pregnancy outside the womb).

My healthcare provider has told me that these symptoms listed above could require emergency care. If I cannot reach the clinic/office/provider right away, my healthcare provider has told me who to call and what to do.
5. I should follow up with my healthcare provider about 7 to 14 days after I take mifepristone to be sure that my pregnancy has ended and that I am well.
6. I know that, in some cases, the treatment will not work. This happens in about 2 to 7 out of 100 women who use this treatment. If my pregnancy continues after treatment with mifepristone and misoprostol, I will talk with my provider about a surgical procedure to end my pregnancy.
7. If I need a surgical procedure because the medicines did not end my pregnancy or to stop heavy bleeding, my healthcare provider has told me whether they will do the procedure or refer me to another healthcare provider who will.
8. I have the MEDICATION GUIDE for mifepristone.
9. My healthcare provider has answered all my questions.

Patient Signature: _____ **Patient Name (print):** _____ **Date:** _____

Provider Signature: _____ **Provider Name (print):** _____ **Date:** _____

Patient Agreement Forms may be provided, completed, signed, and transmitted in paper or electronically.

01/2023

MIFEPREX®(Mifepristone) Tablets, 200mg
PHARMACY AGREEMENT FORM

Pharmacies must designate an authorized representative to carry out the certification process and oversee implementation and compliance with the Mifepristone REMS Program on behalf of the pharmacy.

Healthcare settings, such as medical offices, clinics, and hospitals, where mifepristone will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification.

By signing this form, as the Authorized Representative I certify that:

- Each location of my pharmacy that will dispense Mifeprex is able to receive *Prescriber Agreement Forms* by email and fax.
- Each location of my pharmacy that will dispense Mifeprex is able to ship Mifeprex using a shipping service that provides tracking information.
- I have read and understood the Prescribing Information for Mifeprex. The Prescribing Information is available by calling 1-877-4 EARLY OPTION (1-877-432-7596 toll-free) or online at www.earlyoptionpill.com; and
- Each location of my pharmacy that will dispense Mifeprex will put processes and procedures in place to ensure the following requirements are completed. I also understand that if my pharmacy does not complete these requirements, the distributor may stop accepting Mifeprex orders.
 - Verify that the prescriber is certified in the Mifepristone REMS Program by confirming their completed *Prescriber Agreement Form* was received with the prescription or is on file with your pharmacy.
 - Dispense Mifeprex such that it is delivered to the patient within 4 calendar days of the date the pharmacy receives the prescription, except as provided in the following bullet.
 - Confirm with the prescriber the appropriateness of dispensing Mifeprex for patients who will receive the drug more than 4 calendar days after the date the pharmacy receives the prescription and document the prescriber's decision.
 - Record in the patient's record the NDC and lot number from each package of Mifeprex dispensed.
 - Track and verify receipt of each shipment of Mifeprex.
 - Dispense mifepristone in its package as supplied by Danco Laboratories, LLC.
 - Report any patient deaths to the prescriber, including the NDC and lot number from the package of Mifeprex dispensed to the patient, and remind the prescriber of their obligation to report the deaths to Danco Laboratories, LLC. Notify Danco that your pharmacy submitted a report of death to the prescriber, including the name and contact information for the prescriber and the NDC and lot number of the dispensed product.
 - Not distribute, transfer, loan or sell mifepristone except to certified prescribers or other locations of the pharmacy.
 - Maintain records of *Prescriber Agreement Forms*, dispensing and shipping, and all processes and procedures including compliance with those processes and procedures.
 - Maintain the identity of Mifeprex patients and prescribers as confidential and protected from disclosure except to the extent necessary for dispensing under this REMS or as necessary for payment and/or insurance.
 - Train all relevant staff on the Mifepristone REMS Program requirements.
 - Comply with audits carried out by the Mifepristone Sponsors or a third party acting on behalf of the Mifepristone Sponsors to ensure that all processes and procedures are in place and are being followed.

Any new authorized representative must complete and submit the *Pharmacy Agreement Form*.

Authorized Representative Name: _____ Title: _____



*MIFEPREX is a registered trademark of Danco Laboratories, LLC

P.O. Box 4816-New York, NY 10185

1-877-4-EARLY-OPTION (1-877-432-7596) www.earlyoptionpill.com

Signature: _____ Date: _____

Email: _____ Phone: _____ Preferred ___ email ___ phone

Pharmacy Name: _____

Pharmacy Address: _____

Return completed form to Mifeprex@dancodistributor.com or fax to 1-866-227-3343.



*MIFEPREX is a registered trademark of Danco Laboratories, LLC
P.O. Box 4816-New York, NY 10185
1-877-4-EARLY-OPTION (1-877-432-7596) www.earlyoptionpill.com

PHARMACY AGREEMENT FORM**Mifepristone Tablets, 200 mg**

Pharmacies must designate an authorized representative to carry out the certification process and oversee implementation and compliance with the Mifepristone REMS Program on behalf of the pharmacy.

Healthcare settings, such as medical offices, clinics, and hospitals, where mifepristone will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification.

By signing this form, as the Authorized Representative I certify that:

- Each location of my pharmacy that will dispense mifepristone is able to receive *Prescriber Agreement Forms* by email and fax.
- Each location of my pharmacy that will dispense mifepristone is able to ship mifepristone using a shipping service that provides tracking information.
- I have read and understood the Prescribing Information for mifepristone. The Prescribing Information is available by calling 1-855-MIFE-INFO (1-855-643-3463 toll-free) or online at www.MifeInfo.com; and
- Each location of my pharmacy that will dispense mifepristone will put processes and procedures in place to ensure the following requirements are completed. I also understand that if my pharmacy does not complete these requirements, the distributor may stop accepting mifepristone orders.
 - Verify that the prescriber is certified in the Mifepristone REMS Program by confirming their completed *Prescriber Agreement Form* was received with the prescription or is on file with your pharmacy.
 - Dispense mifepristone such that it is delivered to the patient within 4 calendar days of the date the pharmacy receives the prescription, except as provided in the following bullet.
 - Confirm with the prescriber the appropriateness of dispensing mifepristone for patients who will receive the drug more than 4 calendar days after the date the pharmacy receives the prescription and document the prescriber's decision.
 - Record in the patient's record the NDC and lot number from each package of mifepristone dispensed.
 - Track and verify receipt of each shipment of mifepristone.
 - Dispense mifepristone in its package as supplied by GenBioPro, Inc.
 - Report any patient deaths to the prescriber, including the NDC and lot number from the package of mifepristone dispensed to the patient, and remind the prescriber of their obligation to report the deaths to GenBioPro, Inc. Notify GenBioPro that your pharmacy submitted a report of death to the prescriber, including the name and contact information for the prescriber and the NDC and lot number of the dispensed product.
 - Not distribute, transfer, loan or sell mifepristone except to certified prescribers or other locations of the pharmacy.
 - Maintain records of *Prescriber Agreement Forms*, dispensing and shipping, all processes and procedures including compliance with those processes and procedures.
 - Maintain the identity of mifepristone patients and prescribers as confidential and protected from disclosure except to the extent necessary for dispensing under this REMS or as necessary for payment and/or insurance purposes.
 - Train all relevant staff on the Mifepristone REMS Program requirements.
 - Comply with audits carried out by the Mifepristone Sponsors or a third party acting on behalf of the Mifepristone Sponsors to ensure that all processes and procedures are in place and are being followed.

Any new authorized representative must complete and submit the *Pharmacy Agreement Form*.

Authorized Representative Name: _____ Title: _____

Signature: _____ Date: _____

Email: _____ Phone: _____ Preferred __ email __ phone

Pharmacy Name: _____

Pharmacy Address: _____

Return completed form to RxAgreements@GenBioPro.com or fax to **1-877-239-8036**.



GenBioPro Inc. - PO Box 32011 - Las Vegas, NV 89103
1-855-MIFE-INFO (1-855-643-3463) - www.MifeInfo.com

The REMS Assessment Plan must include but is not limited to the following items.

Program Implementation and Operations

1. REMS Certification Statistics

a. Prescribers

- i. Number of certified prescribers who have certified with the Sponsor's distributor(s) and number who have submitted *Prescriber Agreement Forms* to Certified Pharmacies
- ii. Number and percentage of newly certified prescribers
- iii. Number and percentage of active certified prescribers (i.e., who ordered mifepristone or submitted a prescription during the reporting period)

b. Pharmacies

- i. Number of certified pharmacies
- ii. Number and percentage of newly certified pharmacies
- iii. Number and percentage of active certified pharmacies (i.e., that dispensed mifepristone during the reporting period)

c. Wholesalers/Distributors

- i. Number of authorized wholesalers/distributors
- ii. Number and percentage of newly authorized wholesalers/distributors
- iii. Number and percentage of active authorized wholesalers/distributors (i.e. that shipped mifepristone during the reporting period)

2. Utilization Data

- a. Total number of tablets shipped by wholesalers/distributors, stratified by Certified Prescriber or Certified Pharmacy location
- b. Number of prescriptions dispensed from pharmacies

3. REMS Compliance Data

- a. Audits: Summary of audit activities for each stakeholder (i.e., certified pharmacies and wholesalers/distributors) including but not limited to:
 - i. A copy of the final audit plan for each stakeholder type (provide for the current reporting period)
 - ii. The number of audits expected, and the number of audits performed
 - iii. The number and type of deficiencies noted
 - iv. For those with deficiencies noted, report the corrective and preventive actions (CAPAs) required, if any, to address the deficiencies, including the status (e.g., completed, not completed, in progress) (provide for the current reporting period)
 - v. For any stakeholders that did not complete the CAPA within the timeframe specified in the audit plan, describe actions taken (provide for the current reporting period)

- vi. A summary report of all resulting changes to processes and procedures necessary to ensure compliance with the REMS requirements (provide for the current reporting period)
- b. A summary report of non-compliance, associated corrective action plans (CAPAs), and the status of CAPAs including but not limited to:
 - i. A copy of the final non-compliance plans for Pharmacies and Distributors (provide for the current reporting period)
 - ii. For each instance of noncompliance below (iii-v), report the following information (provide for the current reporting period):
 - 1. A unique, anonymized ID for the stakeholder(s) associated with the non-compliance event to enable tracking over time
 - 2. The source of the non-compliance data (e.g., self-reported, audit, other)
 - 3. A root cause analysis of the non-compliance
 - 4. Actions to prevent future occurrences and outcomes of such actions
 - iii. Prescriber compliance
 - 1. Number and percentage of certified prescribers who became decertified as a result of non-compliance
 - Provide a summary of reasons for decertification (provide for the current reporting period)
 - 2. Summary and analysis of any program deviations and corrective actions taken (provide for the current reporting period)
 - iv. Pharmacy compliance
 - 1. Number and percentage of prescriptions dispensed that were written by prescriber(s) who did not submit a Prescriber Agreement to the dispensing Certified Pharmacy
 - 2. Number and percentage of mifepristone tablets dispensed by non-certified pharmacies
 - 3. Number and percentage of pharmacies that became decertified as a result of non-compliance
 - Provide a summary of reasons for decertification (provide for the current reporting period)
 - 4. An assessment of prescription delivery timelines, including percentage delivered more than four days after receipt of the prescription, duration and causes for delay. A proposal for this assessment will be submitted within 60 days of the approval of the REMS Modification.
 - 5. Summary and analysis of any program deviations and corrective actions taken (provide for the current reporting period)
 - v. Wholesaler/distributor compliance
 - 1. Number of healthcare providers who successfully ordered mifepristone who were not certified
 - 2. Number of non-certified pharmacies that successfully ordered mifepristone
 - 3. Number of shipments sent to non-certified prescriber receiving locations
 - 4. Number of shipments sent to non-certified pharmacy receiving locations

5. Summary and analysis of any program deviations and corrective actions taken (provide for the current reporting period)

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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EXHIBIT H

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
202107Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

RISK MANAGEMENT REVIEW

Date: January 27, 2012

Risk Management Analyst: Suzanne Robottom, Pharm.D.
Division of Risk Management (DRISK)

Team Leader: Cynthia LaCivita, Pharm.D., DRISK

Division Director: Claudia Karwoski, Pharm.D., DRISK

Drug Name: Korlym (mifepristone)

Dosage and Route: 300 mg tablets; by mouth

Application Type/Number: NDA 202-107

Applicant/sponsor: Corcept

OSE RCM #: 2011-2351

EXECUTIVE SUMMARY

The purpose of this review is to document DRISK's determination that a risk evaluation and mitigation strategy (REMS) with elements to assure safe use (ETASU) is not necessary for the approval of mifepristone for the treatment of the signs and symptoms of endogenous Cushing's syndrome.

Corcept submitted a 505(b)(2) application for approval of Korlym (mifepristone) for the treatment of the signs and symptoms of endogenous Cushing's syndrome. Mifepristone (Mifeprex) is currently approved for pregnancy termination with a REMS with ETASU. Based on FDA feedback provided at the September 14, 2010 pre-NDA meeting, Corcept proposed a REMS with ETASU with their NDA submission.

After extensive research and multiple discussions with the review team, DRISK and the Division of Metabolism and Endocrinology Products (DMEP) determined that:

- A REMS with ETASU is not necessary to ensure that the benefits outweigh the risks of Korlym *in the Cushing's population*.
- A REMS with ETASU for Korlym would not improve the benefit/risk balance for the intended use (Cushing's) population and would add burden.
- Use of Korlym outside of Cushing's syndrome cannot be prospectively quantified.

The REMS Oversight Committee and the Center Director provided additional guidance and affirmed that although a REMS is required for Mifeprex, a REMS for Korlym is not necessary to ensure that the benefits of the drug outweigh its risks at this time. Korlym's safety and drug utilization should use be monitored through post marketing requirements (PMR). If data indicate that the current approach compromises the integrity of the Mifeprex REMS and results in serious adverse events, or additional serious safety signals arise, further regulatory action must be considered.

1 INTRODUCTION

The purpose of this review is to document DRISK's determination that a REMS with ETASU is not necessary for the approval of mifepristone for the treatment of the signs and symptoms of endogenous Cushing's syndrome.

1.1 BACKGROUND

Corcept submitted a 505(b)(2) application on April 15, 2011 for approval of Korlym (mifepristone) to treat the clinical and metabolic effects of hypercortisolism in adult patients (≥ 18 years of age) with endogenous Cushing's syndrome including:

- Patients with Cushing's disease who have not adequately responded to or relapsed after surgery
- Patients with Cushing's disease who are not candidates for surgery

(b) (4)

Korlym is manufactured as 300 mg tablets. The proposed dosing for the aforementioned indication is 300 to 1200 mg daily by mouth.

1.2 REGULATORY HISTORY

Mifepristone is currently marketed as Mifeprex and approved on September 28, 2000 under 21 CFR 314 Subpart H for the medical termination of intrauterine pregnancy through 49 days' pregnancy. The approved dosing is 600¹ mg (three (3), 200 mg tablets) followed by misoprostol on Day 4. Since approval, mifepristone is available only through a restricted distribution program that requires prescribers to be enrolled to be able to order Mifeprex and should only be distributed to/through a clinic, medical office, or hospital, by or under the supervision of a specially certified prescriber. Mifeprex is not distributed to or dispensed through retail pharmacies. The restricted distribution program was approved as a REMS on June 8, 2011.²

In 2007, Corcept initiated a clinical development program to evaluate the clinical benefit of mifepristone in patients with Cushing's syndrome and received orphan drug designation on July 5, 2007.

A pre-NDA meeting with Corcept was held on September 14, 2010. Corcept informed the FDA that they intended to submit a REMS and requested comments on the draft REMS. The FDA informed Corcept that for this NDA/indication, a REMS with restricted distribution would be necessary to address the risk of termination of pregnancy. The proposed REMS must be sufficient to maintain the integrity of the current Mifeprex restricted distribution program. The sponsor was instructed that a complete review of the proposed REMS, and REMS materials would be done in conjunction with the full clinical review after the NDA is submitted.

On April 15, 2011 Corcept submitted NDA 202107 for review with a proposed REMS.

2 MATERIALS REVIEWED

The following materials were reviewed:

- Weber J. Pre-NDA Meeting Preliminary Comments for September 14, 2010. Signed under IND 76480 on September 9, 2010 by Weber J.
- NDA 202107 submitted on April 15, 2011 and received on April 18, 2011 with a proposed REMS with ETASU.
- Bhatnagar U. Maternal Health Team review for Mifepristone. Signed September 15, 2011 by Bhatnagar U, Feibus K, and Mathis L.
- Greene P. Drug use review of Mifeprex. Signed September 19, 2011 by Greene P, Chai G, and Governale L.

¹ Standard practice is to dispense a single, 200 mg tablet of mifepristone, not 600 mg. In addition, the standard misoprostol dose is 800µg (4 tablets), not 400 µg.

² Mifepristone was included on the list of products deemed to have in effect an approved risk evaluation and mitigation strategy (REMS) under section 505-1 of the Federal Food, Drug, and Cosmetic Act with the passage of the Food and Drug Administration Amendments Act (FDAAA) of 2007.

- November 3, 2011 Center Director Briefing on Mifepristone for Cushing's syndrome. Signed into DAARTS for NDA 202107 on November 15, 2011 by Egan A.
- (b) (6) Division of Reproductive and Urology Products consult response. Signed November 18, 2011 by (b) (6).

3 RISK BENEFIT CHARACTERIZATION

3.1 CUSHING'S SYNDROME AND TREATMENT OPTIONS

Cushing's syndrome is a serious, multisystem disorder that results from overproduction of cortisol by the adrenal glands. For those not cured by surgery, it is a chronic and debilitating condition.⁴ If left untreated, Cushing's syndrome limits survival to 4 to 5 years following initial diagnosis.³

Surgical resection of the offending tumor remains first line treatment, and initial cure or remission is obtained in 65-85% of patients with Cushing's disease.⁴ In cases that surgery only partially or temporarily controls glucocorticoid hypersecretion (or for patients who are not candidates for surgery),⁵ radiation and/or pharmacologic treatment is used for disease control. A two to three fold increase in mortality is observed in most studies and this excess mortality seems confined to patients in whom initial cure was *not* obtained (the indicated population for mifepristone).⁴

There is an unmet medical need for additional drug treatment options for Cushing's syndrome. The following table lists the drug treatment options, none of which are approved for Cushing's syndrome:^{2,6}

Steroidogenic inhibition	Adrenolytic	Neuromodulators of ACTH release	Glucocorticoid receptor antagonism
<ul style="list-style-type: none"> • Metyrapone (not available in US) • Aminogluthethimide (discontinued)[^] • Ketoconazole 	<ul style="list-style-type: none"> • Mitotane^{^^} • Etomidate 	<ul style="list-style-type: none"> • Cyproheptidine* • Bromocriptine* • Valproic acid* • Octreotide* 	<ul style="list-style-type: none"> • Mifepristone
[^] Aminogluthethimide was approved in 1980 and indicated "for the the suppression of adrenal function in selected patients with Cushing's syndrome." ^{^^} Mitotane was approved in 1970 and indicated for "the treatment of inoperable adrenal cortical carcinoma of both functional and nonfunctional types." *Agent has <u>not</u> demonstrated consistent clinical efficacy. ³			

³ Gums JG, Smith JD. Adrenal Gland Disorders. Pharmacotherapy: A pathophysiologic approach. 4th ed. Ed Dipiro JT. Stamford, Appleton & Lange, 1999. Print.

⁴ Steffensen C, Bak AM, Rubeck KZ, Jorgensen JO. Epidemiology of Cushing's syndrome. Neuroendocrinology 2010;92(supp 1):1-5.

⁵ Johanssen S, Allolio B. Mifepristone (RU 486) in Cushing's syndrome. Euro J Endocrin (2007)156; 561-569.

⁶ Heyn J, et al. Medical suppression of hypercortisolemia in Cushing's syndrome with particular consideration for etomidate. Pituitary (online May 10, 2011).

3.1.1 Size of Population

Cushing's syndrome is a rare disorder with incidence ranging from 0.7 to 2.4 per 1 million persons per year.⁷ Ninety percent of all cases of Cushing's syndrome occur during adulthood; the incidence of Cushing's syndrome in children is estimated at approximately 0.2 cases per 1 million persons per year.

It is estimated that at any given time there are approximately 20,000 patients with Cushing's syndrome in the U.S. The peak incidence of Cushing's syndrome due to an adrenal or pituitary tumor occurs in persons 25-40 years of age; females are 8 times more likely than males to develop hypercortisolemia from a pituitary tumor and 3 times more likely to develop a cortisol-secreting adrenal tumor.

In the US, it is estimated that approximately 5,000 patients would be considered candidates for treatment with Korlym.

3.2 EXPECTED DRUG BENEFIT

Mifepristone works by binding to glucocorticoid receptors, preventing cortisol from binding, and thereby blocking cortisol's activity and effects. It does not decrease the amount of circulating cortisol. It has a rapid onset of action (~90 minutes for peak plasma concentrations).

According to the sponsor in Study 400 (open label, 24 week prospective trial), 60% of the diabetes patients met the primary endpoint of at least a 25% reduction in AUC_{glucose}, and antidiabetic medication use was reduced in half of the patients. The Data Review Board determined that 72% of patients met the secondary endpoint of a change in signs and symptoms at week 24.

Mifepristone may be used as an adjunct to radiation, palliative treatment, or when rapid onset of anti-glucocorticoid effect is required (e.g., psychosis).

3.3 DURATION OF TREATMENT

Cushing's syndrome that is not cured by surgery is a chronic condition. Patients may be treated indefinitely (weeks, months, years/decades) with mifepristone.

3.4 SEVERITY OF THE RISK

The observed risks (adverse events documented in the safety database; adrenal insufficiency, hyopkalemia, and endometrial hyperplasia) in patients with Cushing's syndrome were considered. After discussion with DMEP, we agree that these risks can be adequately addressed through labeling.

⁷ Newell-Price J, Bertagna X, Grossman AB, Nieman LK. Cushing's syndrome. Lancet. 2006 May 13;367(9522):1605-17.

Two risks were identified that are anticipated to occur in the post-marketing setting. These risks were the focus of the risk management discussion.

3.4.1 Fetal Loss (unintended pregnancy termination)

3.4.1.1 Cushing's Syndrome Patients

Mifepristone blocks progesterone receptors at lower doses than necessary for glucocorticoid receptor inhibition. Therefore, the lowest treatment dose studied for the treatment of Cushing's syndrome is effective for terminating pregnancy. However, mifepristone alone is less effective for pregnancy termination when compared to the combined regimen mifepristone/prostaglandin.⁸

Women with Cushing's syndrome are not at substantial risk for fetal loss because they are unlikely to be pregnant. The review by the Maternal Health Team (MHT) states that amenorrhea and ovulatory disturbances are associated with untreated Cushing's syndrome and therefore pregnancy occurs "rarely" in this population. Pregnancy may occur in a small subset of patients with Cushing's syndrome who are of childbearing age. MHT recommends that this possibility be noted in labeling.⁹

At the time treatment is initiated with mifepristone, a woman has a low likelihood of conception due to her underlying disease. During treatment, if she is not compliant with mifepristone treatment, she would be amenorrheic due to worsened disease condition. If she is compliant with medication, mifepristone would prevent a sustained pregnancy. Therefore, the risk of fetal loss before and during treatment in the intended patient population appears low.

Pregnancy tests were performed in Study 400 as part of enrollment and repeated after any significant interruption of treatment. No pregnancies were reported.

3.4.1.2 Non-Cushing's Syndrome Patients

There are a variety of uses for mifepristone (b) (4). It has been studied to treat the following:

(b) (4)

(b) (4)

⁸ (b) (6) Division of Reproductive and Urology Products consult response. Signed November 18, 2011 by (b) (6)

⁹ Bhatnagar U. Maternal Health Team review for Mifepristone. Signed September 15, 2011 by Bhatnagar U, Feibus K, and Mathis L.

At present, mifepristone is only commercially available in blister packages (3 pills per carton) that are sold through the Mifeprex REMS. If Korlym is approved without restrictions (e.g. REMS), mifepristone will be more readily available to treat females of child bearing potential with other chronic conditions. The extent of off-label use of mifepristone, for the above conditions, in the post-marketing setting is unknown.

3.4.2 Intended Termination of Pregnancy with Korlym

If Korlym is approved without a REMS with restricted distribution, there will be increased access to mifepristone. This could lead to 1) prescribers prescribing Korlym for the termination of pregnancy without following the safeguards that are in place for Mifeprex and/or 2) misuse, pilfering, and diversion of Korlym for the termination of pregnancy not under the supervision of a healthcare provider.

The risk mitigation tools for the Mifeprex REMS are physician certification and controlled access to assure safe use. A Mifeprex prescriber must agree that he/she meets the required qualifications to assure the drug is used safely and appropriately. Compliance with the REMS requirements is not enforced beyond a one-time completion of the enrollment form (e.g., signed Patient Agreements are not collected). The certification requirement is the tool that provides controlled access for Mifeprex. Without restricted distribution, a prescriber using Korlym for pregnancy termination would not have to attest to having certain skills, agree to document certain information/activities, or report adverse events. The patient would not receive a Patient Agreement or Mifeprex Medication Guide that would provide the most relevant and important information to her for pregnancy termination. The current REMS does not prevent use beyond 49 days gestation, termination of an ectopic pregnancy, bleeding, incomplete abortion, and infection.

In considering if there is increased potential for pilfering and misuse with Korlym, we note that Mifeprex is distributed only to medical facilities and dispensed to the patient in small quantities (a single tablet) by certified prescribers. Korlym will be distributed directly to patients, in larger quantities and each Korlym tablet is an effective dose for pregnancy termination. Moreover, Korlym is proposed to be packaged in bottles of 28 and 280, making diversion and pilfering presumably easier relative to the Mifeprex packaging. Similar to Korlym, there is potential for Mifeprex to be pilfered or diverted from a distribution facility, during shipping, or at the place of dispensing. Mifeprex has processes in place to prevent drug loss during distribution and shipping that can be done outside a REMS for Korlym. It is not known if clinics keep careful stock and dispensing records of Mifeprex.

3.5 RISK IN CONTEXT OF DRUGS IN CLASS AND AMONG OTHER DRUGS USED TO TREAT THE DISEASE

There are no other glucocorticoid receptor antagonists approved in the U.S. for comparison.

Ketoconazole, metapyrone (not approved in U.S.), mitotane, etomidate are anti-corticoid drugs that are used for the treatment of Cushing's syndrome. Because these drugs have a

different mechanism of action, they are not associated with the same potential risks as mifepristone. These drugs are associated with serious risk(s) although none of these drugs have a REMS.

3.6 HOW THE RISK(S) ARE MANAGED ACROSS OTHER PRODUCTS AND/OR DISEASES

3.6.1 Fetal Loss

Other drug products are associated with fetal loss (e.g., methotrexate, misoprostol; see Attachment 1). At present, this risk is addressed through labeling for these drugs. There are no REMS approved that address only fetal loss without also the accompanying risk of birth defect.

3.6.2 Intended Termination of Pregnancy with Korlym

We identified two drugs, misoprostol and methotrexate, that are associated with a risk of pregnancy termination and are approved for other uses. See the table in Attachment 1. The extent to which misoprostol and methotrexate are used off-label to terminate pregnancy is unknown. With each drug, the risk of termination of pregnancy is managed through labeling (Contraindication, Boxed Warning) and neither product has a REMS.

3.6.3 Misuse

Misuse has been addressed in different ways as follows:

Voluntary Restricted Distribution:

- *Example: Egrifta/growth hormone:* Growth hormones are at risk for misuse and abuse. None of the growth hormone products have a REMS. However, the sponsor has voluntarily decided to distribute this product through a non-REMS restricted distribution system which allows tracking “of each box of Egrifta to determine the volume of product dispensed and evaluate if the projected number of boxes dispensed correlates with prescription use in the intended population.”¹⁰ Egrifta was approved in 2010 with no REMS and no PMR for monitoring drug use.

Required Restricted Distribution Program

- *Example: Xyrem*¹¹
 - At the time Xyrem was initially approved in 2002, the Sponsor agreed as a condition of approval to distribute and dispense Xyrem through a primary and exclusive central pharmacy, implement a program to educate physicians and patients about the risks and benefits of Xyrem, fill the initial prescription only after the prescriber and patient received and read the educational materials, and maintain patient and prescribing physician registries.¹²

¹⁰ LaCivita C. Review of REMS for Egrifta. Signed September 3, 2010.

¹¹ Xyrem was included on the list of products deemed to have in effect an approved risk evaluation and mitigation strategy (REMS) under section 505-1 of the Federal Food, Drug, and Cosmetic Act with the passage of the Food and Drug Administration Amendments Act (FDAAA) of 2007.

¹² Choudhry Y. REMS Interim Comment Set #1. Signed August 1, 2011 by Choudhry Y and Worthy K.

3.6.4 Same Active Ingredient, Different Indication and Different Risk Management Approaches

The agency evaluates an active ingredient based on the risk benefit profile for the intended population. To date, the Agency has not required a REMS for a product based only on the fact that the active ingredient already has a REMS for one population. For example, denosumab was originally approved under two tradenames for different indications. Prolia was initially approved for the treatment for post-menopausal osteoporosis (PMO). At that time, a REMS for Prolia was required and approved consisting of a Medication Guide and communication plan to “inform healthcare providers about the risks of serious infections, dermatologic adverse reactions, and suppression of bone turnover, including osteonecrosis of the jaw.” Under the tradename Xgeva, denosumab was approved for prevention of skeletal-related events in patients with bone metastases from solid tumors. A REMS was not required given the resulting differences in the risk benefit profile when considering the patient populations (post-menopausal women vs cancer patients with bone metastases) and prescribing populations (internists vs oncologists).

3.7 PRODUCTS AFFECTED

Mifeprax (and pending generics) are potentially affected because they are or will only be available under a restrictive REMS.

4 RISK MANAGEMENT CONSIDERATIONS

The following factors are important to consider:

- Burden to the intended population

It is important to ensure that the intended treatment population can receive Korlym in a timely, dependable manner in the least burdensome way. Any restrictions will impede access with little to no benefit to Cushing’s syndrome population.

- Confidentiality/Privacy

Confidentiality and patient privacy is a significant issue with Mifeprax. To what extent do stakeholders who make, distribute, dispense, prescribe, and use Korlym need protection from a confidentiality perspective?

The purpose of a REMS is to ensure the benefits of the drug outweigh its risks. Confidentiality and concern regarding the safety of the prescribers, pharmacists, and patients does not meet criteria. Confidentiality can be maintained without a REMS. Privacy may be better maintained if there are no systems in place to track formally prescribers and patients. Risk to pharmacies that stock the drug should be considered but it is outside the purview of a REMS.

- Reproductive potential for various possible Korlym off-label use populations

As stated in section 3.4.1.2. above, there are a variety of uses for mifepristone (b) (4). The therapeutic areas included below are more likely to include females of reproductive potential than other uses (b) (4). A formal epidemiologic review was not conducted to estimate of the proportion of females of reproductive potential for each use. However, the following observations and/or assumptions were made:



The degree to which Korlym will be used off label for the above uses is unknown.

- Extent of current off-label use

Current Mifeprex drug utilization information is not informative in predicting broader uses for Korlym. In the September 19, 2011 mifepristone drug use review using commercial databases was conducted, off-label use was described as “uncommon” based on information obtained through a *sample* of medical offices and outpatient clinics. Sales distribution data was not available. The lack of findings are not surprising given the design of the Mifeprex REMS.

5 RISK MANAGEMENT OPTIONS

DRISK analyzed more than six risk management options to address intended termination of pregnancy by:

- HCPs outside of Mifeprex REMS
- women who seek to terminate a pregnancy and are not under the care of an HCP

Ultimately, three options were considered.

1. No REMS and voluntary restricted distribution through specialty pharmacies/distributors

This REMS option may minimize diversion and subsequent misuse by minimizing the number of pharmacies stocking and dispensing Korlym for outpatient use. This option is in alignment with DMEP and DRISK’s assessment that a REMS is not necessary to assure the safe use of mifepristone for treating patients with Cushing’s syndrome because we believe the likelihood that a Cushing’s patient experiences “serious complications” relating to pregnancy termination are low.

This approach is also consistent with misoprostol and methotrexate, both of which are known abortifacents and do not have a REMS to address that risk. This approach is used to prevent misuse of the growth hormone products.

2. REMS with ETASU – dispensing through certified specialty pharmacies

This REMS option may minimize diversion and subsequent misuse by minimizing the number of pharmacies stocking and dispensing Korlym for outpatient use. In addition, Corcept would be required to provide FDA an assessment of how the REMS is achieving its goals.

This option does not address intended termination of pregnancy with Korlym.

3. REMS with ETASU – prescriber certification (agreement not to use for termination of pregnancy) and distribution through certified specialty pharmacies that are willing to track inventory

This REMS option would minimize diversion and subsequent misuse as described above. In addition, certified pharmacies (for outpatient dispensing, not inpatient hospital pharmacies) would verify that prescribers were certified. Prescriber certification would consist of agreement not use Korlym for pregnancy termination. The addition of prescriber certification would address the risk of intended termination of pregnancy with Korlym.

These options assume that the safety labeling is maximized to address Korlym use in pregnancy.

6 DISCUSSION

The issue of how to address intended termination of pregnancy was discussed at the REMS Oversight Committee meeting on September 29, 2011 and at a Center Director Briefing on November 3, 2011.

DMEP and DRISK presented at both meetings that women with Cushing's syndrome are unlikely to be or become pregnant given the effects of their disease on the reproductive system and the effects of daily mifepristone treatment. Therefore, addressing the risk of fetal loss associated with Korlym was not discussed because 1) pregnancy is not a likely event in the intended population and; 2) the use of Korlym for "off-label" uses (in women more likely to be pregnant) is unknown and available data do not indicate that mifepristone would be first line treatment for any diseases or conditions at this time. For these reasons, there was general agreement that fetal loss can be adequately addressed through labeling and is not necessary to require additional safe use measures through a REMS at this time.

The team stated that for any risk management approach, it is important to ensure that the intended treatment population can receive Korlym in a timely, dependable manner in the least burdensome way. Any restrictions could impede access without benefit to the intended population.

The primary focus shifted to whether or not a REMS is necessary for Korlym to maintain the integrity of the Mifeprex REMS. While the absence of any restrictions on Korlym could undermine the safe use conditions required by the Mifeprex REMS, a number of other factors are important considerations including:

- The burden (reduced access, treatment delays) of a restrictive REMS to the Cushing's population without any benefit from the REMS for this population.
- Overall drug exposure and subsequent access is anticipated to be small given the small size of the intended use population and lack of a signal for substantially broader use.
- The sponsor's plan to distribute Korlym through a specialty pharmacy regardless of the REMS. If necessary, this provides the sponsor the ability to monitor use more closely.
- The cost - If the cost of this orphan product is substantial, it may be expensive to obtain and deter use for pregnancy termination as well as other off label uses. In addition, third party payors/reimbursement may play a substantial role in influencing prescribing behavior. It is unknown how much Korlym will cost and how cost will impact prescribing behavior.¹³

The need for some monitoring of use was discussed. Commercial drug use databases will not provide FDA with adequate estimates of Korlym use because Korlym will be dispensed through a specialty pharmacy. As noted above, using a single specialty pharmacy does allow the sponsor the ability to monitor use more closely through its business contract with the specialty pharmacy. Similarly, commercial drug use databases are not able to provide an accurate estimate of Mifeprex use due to how it is distributed and dispensed. The first REMS assessment for Mifeprex is due June 2012 which we anticipate will provide a baseline to quantify current Mifeprex use. Given these considerations and the discussion with the Center Director, we agree that a post-marketing requirement (PMR) study to obtain Korlym use data (age, gender, dose, duration of treatment) "to better characterize the incidence rates of adverse events with Korlym" is prudent. Monitoring drug use data for both Mifeprex and Korlym, in conjunction with reports of serious adverse events resulting from pregnancy terminations outside of the Mifeprex REMS, will be important factors in future regulatory action to address any compromise to the Mifeprex REMS.

7 CONCLUSION

A REMS for Korlym is not necessary to ensure that the benefits of the drug outweigh its risks at this time. We agree that it is prudent to monitor use through a PMR. If data indicate that this approach compromises the integrity of the Mifeprex REMS and results in serious adverse events, or additional serious safety signals arise, further regulatory action must be considered.

ATTACHMENTS

¹³ Planned parenthood charges \$300-800 for a medical abortion (includes diagnostic testing, mifepristone, and misoprostol).

ATTACHMENT 1: Drugs with a risk associated with an off-label use

Drug	Abortifacient Efficacy	Indication	Off-label use*	Contraindication	Boxed Warning
Misoprostol (Cytotec)	When used alone – variable (~40-60%); used in combination with MTX or MFP efficacy is higher (Source - Micromedex)	NSAID-induced gastric ulcers	<ul style="list-style-type: none"> • Postpartum hemorrhage • Cervical ripening, labor induction • Pregnancy termination 	“Cytotec should not be taken by pregnant women to reduce the risk of ulcers induced by NSAIDs ”	“Cytotec administration to women who are pregnant can cause abortion ... Cytotec should not be taken by pregnant women to reduce the risk of ulcers induced by NSAIDs... Patients must be advised of the abortifacient property and warned not to give the drug to others ... ”
Methotrexate (MTX)	When used alone – (IM injxn – variable); in combination with misoprostol efficacy is higher (80-90%; small Ns) (Source - Micromedex)	<ul style="list-style-type: none"> • Cancer • Psoriasis • Rheumatoid arthritis including juvenile 	<ul style="list-style-type: none"> • Other Autoimmune diseases • More cancer • Pregnancy termination 	“MTX can cause fetal death or teratogenic effects when administered to a pregnant woman MTX is contraindicated in pregnant women with psoriasis or rheumatoid arthritis and should be used in the treatment of neoplastic diseases only when the potential benefit outweighs the risk to the fetus Women of childbearing potential should not be started on MTX until pregnancy is excluded and should be fully counseled on the serious risk to the fetus should they become pregnant while undergoing treatment ”	“MTX has been reported to cause fetal death and/or congenital anomalies Therefore, it is not recommended for women of childbearing potential unless there is clear medical evidence that the benefits can be expected to outweigh the considered risks Pregnant women with psoriasis or rheumatoid arthritis should not receive MTX ”

*The off-label uses are general and based on tertiary sources; not on a formal drug use analysis.

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/s/

SUZANNE C BERKMAN ROBOTOM
01/27/2012

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01/27/2012
concur

EXHIBIT I

REMS: FDA's Application of Statutory Factors in Determining When a REMS Is Necessary

Guidance for Industry

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)**

**April 2019
Drug Safety**

REMS: FDA's Application of Statutory Factors in Determining When a REMS Is Necessary Guidance for Industry

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**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)**

**April 2019
Drug Safety**

Contains Nonbinding Recommendations

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Contains Nonbinding Recommendations

REMS: FDA’s Application of Statutory Factors in Determining When a REMS Is Necessary

Guidance for Industry¹

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to clarify how the Food and Drug Administration (FDA or Agency) applies the factors set forth in section 505-1 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355-1) in determining whether a risk evaluation and mitigation strategy (REMS) is necessary to ensure that the benefits of a drug outweigh its risks.² This guidance fulfills one of the performance goals that FDA agreed to satisfy in the reauthorization of the Prescription Drug User Fee Act (PDUFA) V.³

FDA’s guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in agency guidances means that something is suggested or recommended, but not required.

¹ This guidance has been prepared by the Office of New Drugs, Office of Surveillance and Epidemiology, Office of Medical Policy, and Office of Regulatory Policy in the Center for Drug Evaluation and Research (CDER), in cooperation with the Center for Biologics Evaluation and Research (CBER), at the Food and Drug Administration.

² Section 505-1 of the FD&C Act applies to applications for prescription drugs submitted or approved under subsections 505(b) (i.e., new drug applications) or (j) (i.e., abbreviated new drug applications) of the FD&C Act and to applications submitted or licensed under section 351 (i.e., biologics license applications) of the Public Health Service Act (PHS Act) (42 U.S.C. 262). For the purposes of this document, unless otherwise specified, the term *drug* refers to human prescription drugs, including those that are licensed as biological products (biologics).

³ Section XI.A.1 of “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 Through 2017” (PDUFA V), available at <http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>.

*Contains Nonbinding Recommendations***II. BACKGROUND**

The Food and Drug Administration Amendments Act of 2007 (FDAAA)⁴ created section 505-1 of the FD&C Act, which establishes FDA's REMS authority. A REMS is a required risk management plan that can include one or more elements to ensure that the benefits of a drug outweigh its risks.⁵

If FDA determines that a REMS is necessary, the Agency may require one or more REMS elements, which could include a Medication Guide,⁶ a patient package insert,⁷ and/or a communication plan.⁸ FDA may also require elements to assure safe use (ETASU) as part of a REMS.⁹ ETASU may be required if the drug has been shown to be effective, but is associated with a specific serious risk and can be approved only if, or would be withdrawn unless, such elements are required as part of a strategy to mitigate a specific serious risk(s) listed in the labeling of the drug. ETASU may be required for approved drug products that were initially approved without ETASU when other elements are not sufficient to mitigate a serious risk.

Specifically, ETASU may include one or any combination of the following requirements¹⁰:

- Health care providers who prescribe the drug have particular training or experience, or are specially certified;
- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified;
- The drug be dispensed to patients only in certain health care settings, such as hospitals;
- The drug be dispensed to patients with evidence or other documentation of safe use conditions, such as laboratory test results;
- Each patient using the drug be subject to monitoring; or
- Each patient using the drug be enrolled in a registry.

If a REMS includes certain ETASU, the REMS may also include an implementation system to enable the applicant to monitor, evaluate, and improve the implementation of the elements (e.g., development of a REMS specific Web site or call center to facilitate enrollment; establishment of electronic databases of certified health care settings).¹¹

⁴ Public Law 110-85.

⁵ See section 505-1(e) of the FD&C Act and section 505-1(f) of the FD&C Act.

⁶ See Section 505-1(e)(2) of the FD&C Act.

⁷ Id.

⁸ See Section 505-1(e)(3) of the FD&C Act.

⁹ See Section 505-1(f) of the FD&C Act.

¹⁰ See Section 505-1(f)(3) of the FD&C Act.

¹¹ See Section 505-1(f)(4) of the FD&C Act.

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All REMS should include one or more overall goals, and if the REMS has ETASU, the REMS must include one or more goals to mitigate a specific serious risk listed in the labeling of the drug and for which the ETASU are required.¹²

Finally, REMS generally must include a timetable for submission of assessments of the REMS.¹³ The timetable for submission of assessments of the REMS must include an assessment by the dates that are 18 months and 3 years after the REMS is initially approved, and an assessment in the 7th year after the REMS is approved, or at another frequency specified in the REMS.¹⁴

FDA can require a REMS before initial approval of a new drug application or, should FDA become aware of new safety information¹⁵ about a drug and determine that a REMS is necessary to ensure that the benefits of the drug outweigh its risks, after the drug has been approved.¹⁶

Before FDAAA was enacted, FDA approved a small number of drugs and biologics with risk minimization action plans (RiskMAPs).¹⁷ A RiskMAP is a strategic safety program designed to meet specific goals and objectives in minimizing the known risks of a drug while preserving the drug's benefits. RiskMAPs were developed for products that had risks that required additional risk management strategies that went beyond the provision of FDA-approved labeling, including the prescribing information.¹⁸ In 2005, FDA issued a guidance for industry, *Development and Use of Risk Minimization Action Plans* (RiskMAP Guidance).¹⁹ Many of the principles described in the RiskMAP Guidance are reflected in the REMS provisions set forth in FDAAA²⁰ and have been incorporated into FDA's REMS decision-making process. The purpose of this new guidance is to explain FDA's current application of previously articulated risk management principles and considerations under the REMS regulatory paradigm.

¹² See Section 505-1(f)(3) of the FD& C Act.

¹³ New Drug Applications (NDAs) and Biologics License Applications (BLAs) must include a timetable for submission of assessments. ANDAs are not subject to the requirement for a timetable for submission of assessments (Section 505-1(i)), but FDA can require any application holder, including ANDA applicants, to submit REMS assessments under Section 505-1(g)(2)(C).

¹⁴ See Section 505-1(d); see also 505-1(g)(2) of the FD&C Act.

¹⁵ Section 505-1(b)(3) of the FD&C Act.

¹⁶ See section 505-1(a)(2) of the FD&C Act.

¹⁷ Some of these drugs were approved pursuant to either subpart H (21 CFR 314.520) or subpart E (21 CFR 601.42) with restrictions on their use or distribution to assure safe use.

¹⁸ A drug's *prescribing information* (PI) contains a summary of the essential scientific information needed for the safe and effective use of the drug. 21 CFR 201.56(a)(1). The PI is updated from time to time to incorporate information from postmarketing surveillance or studies, for example, revealing new benefits or risk concerns.

¹⁹ The RiskMAP Guidance is available at <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm071616.pdf>.

²⁰ See section 505-1(a)(1) of the FD&C Act.

*Contains Nonbinding Recommendations***III. MANAGING DRUG RISKS**

The statutory standard for FDA approval of a drug is that the drug is safe and effective for its labeled indications under its labeled conditions of use.²¹ FDA's determination that a drug is safe, however, does not suggest an absence of risk. Rather, a drug is considered to be safe if the clinical significance and probability of its beneficial effects outweigh the likelihood and medical importance of its harmful or undesirable effects. In other words, a drug is considered safe if it has an appropriate benefit-risk balance.

Risk management is a key factor in FDA's risk-benefit assessment.²² As described in previous guidances, risk management consists of both risk assessment and risk minimization: it is an iterative process involving (1) assessing a drug's benefit-risk balance, (2) developing and implementing tools to minimize the drug's risks while preserving its benefits, (3) evaluating tool effectiveness and reassessing the benefit-risk balance, and (4) making adjustments, as appropriate, to risk minimization tools to further improve the benefit-risk balance. This four-part process should be continuous throughout a drug's life cycle, with the results of risk assessment informing the sponsor's decisions regarding risk minimization.²³

IV. THE USE OF REMS IN MANAGING DRUG RISKS

The goal of risk mitigation is to preserve a drug's benefits while reducing its risks to the extent possible. For the majority of drugs, routine risk mitigation measures, such as providing health care providers with risk information through FDA-approved prescribing information, are sufficient to preserve benefits while minimizing risks. In some cases, however, FDA may consider whether a REMS would help ensure that the benefits of the drug outweigh its risks.

FDA's determination as to whether a REMS is necessary for a particular drug is a complex, drug-specific inquiry, reflecting an analysis of multiple, interrelated factors and of how those factors apply in a particular case. In conducting this analysis, FDA considers whether (based on premarketing or postmarketing risk assessments) there is a particular risk or risks associated with the use of the drug that, on balance, outweigh its benefits and whether additional interventions beyond FDA-approved labeling are necessary to ensure that the drug's benefits outweigh its risks.

In making these determinations, FDA may take into consideration information from a variety of sources, including FDA's internal and external experts with specialized expertise relevant to a particular risk, input on relevant issues from other centers within FDA, other government

²¹ See section 505(d) of the FD&C Act (21 U.S.C. 355(d)).

²² Information about FDA's Benefit-Risk Assessment Framework is available at <https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm>

²³ See the following FDA guidances for industry: *Premarketing Risk Assessment*, available at <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm072002.pdf>; RiskMAP Guidance; and *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment*, available at <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm071696.pdf>.

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agencies, advisory committee meetings, the Drug Safety Oversight Board, literature, and professional societies. For approved drugs, FDA may also gather information from post-approval adverse event reports and active surveillance, as well as from post-approval clinical trials and other post-approval studies, including epidemiological studies, when evaluating whether a REMS is necessary.

If FDA determines that a REMS is necessary, the Agency considers what the goals of a proposed REMS to address these risks would be and what specific REMS elements, as described above, could help meet those goals. The REMS should be designed to meet the relevant goals, not unduly impede patient access to the drug, and minimize the burden on the health care delivery system to the extent practicable. If FDA believes that the drug's risks would exceed its benefits even if FDA were to require a REMS for the drug, FDA will not approve the drug or may consider seeking withdrawal of the drug if it is already being marketed.

V. APPLICATION OF STATUTORY FACTORS IN REMS DECISION-MAKING

Section 505-1(a)(1) of the FD&C Act, as added by FDAAA, requires FDA to consider the following six factors²⁴ in making a decision about whether to require a REMS:

- The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- The expected benefit of the drug with respect to the disease or condition;
- The seriousness of the disease or condition that is to be treated with the drug;
- Whether the drug is a new molecular entity;
- The expected or actual duration of treatment with the drug; and
- The estimated size of the population likely to use the drug.

These six factors influence FDA's decisions with respect to whether a REMS is required for a particular drug and what type of REMS might be necessary (i.e., what specific elements or tools should be included as part of the REMS). FDA makes decisions about requiring a REMS as part of a benefit-risk determination for a drug after an evaluation that includes integrated consideration of each of the statutory factors. All six factors are considered together to inform FDA's REMS decision making process and no single factor is determinative as to whether a REMS is necessary. The relative importance or weight of each factor is a case specific inquiry. The application of these factors is discussed in the sections below.

²⁴ The FD&C Act requires that FDA consider these factors in determining whether a REMS is necessary for a new drug. FDA also generally considers these factors in determining whether (based on new safety information) a REMS is necessary for a drug that is the subject of an approved application.

*Contains Nonbinding Recommendations***A. Seriousness of Known or Potential Adverse Events That May Be Related to the Drug and the Background Incidence of Such Events in the Population Likely To Use the Drug**

The more serious²⁵ a drug's known or potential associated risks relative to its benefits, the more likely it is that a REMS will be necessary to ensure that the benefits of the drug outweigh its risks. In determining whether to require a REMS, FDA considers the source, nature and reliability of available scientific evidence about the adverse events as well as the characteristics of the risks, including the reversibility, preventability, temporality, frequency, severity, background incidence, and likelihood of occurrence.

For drugs associated with adverse events that are reversible or preventable if particular measures are taken promptly, FDA may consider requiring a REMS to help ensure that such measures are undertaken in a timely manner to minimize or prevent a serious adverse event. For example, for a drug that is associated with hepatotoxicity that is reversible with drug discontinuation, the REMS may require that the patient be monitored through laboratory studies so that the drug can be discontinued if and when hepatic enzyme elevations are observed.

A drug that is associated with a risk of a serious adverse event that is irreversible, such as one that causes a permanent disability or persistent incapacity, may be particularly likely to have a favorable benefit-risk profile only in the presence of a REMS that helps minimize drug exposure and the associated occurrence of the adverse event. In such cases, a REMS may include, for example, a prescriber certification requirement that includes prescriber training and patient counseling on the nature of the associated risk and on the drug's benefit-risk balance to facilitate informed patient and prescriber decisions about treatment with the drug. Such REMS are designed to ensure that patients are fully informed of the serious risk before beginning therapy and may involve patient acknowledgment forms or other methods of documenting that such patient-provider discussions have taken place. This kind of REMS is particularly important for drugs with limited available methods of preventing the actual occurrence of drug-associated adverse events.

The frequency and severity of adverse events associated with the use of a drug may also affect FDA's determination of whether a REMS is necessary. While a high frequency of adverse events may necessitate a REMS to mitigate this risk, FDA may also require a REMS for an infrequent adverse event, if the adverse event is particularly severe.

As part of its assessment of whether a particular adverse event is drug-associated, FDA examines the rate of the adverse event in individuals exposed to the drug relative to the background incidence of the adverse event in the population likely to use the drug. If an adverse event is determined to be drug-associated, FDA may determine that treatment with the drug unacceptably

²⁵ Section 505-1(b)(4) of the FD&C Act defines an adverse drug experience as serious if it results in death, immediate risk of death, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect (or, based on appropriate medical judgment, may jeopardize the patient and may require a medical or surgical intervention to prevent the above-described outcomes).

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increases the frequency and/or severity of the adverse event in the patient population and that this risk needs to be mitigated through a REMS.

As part of its evaluation of the risks associated with the use of a drug, FDA also takes into consideration whether information about managing the particular risk is widely available and whether risk management measures are being widely implemented. FDA may also consider factors such as the specialties of the healthcare providers who may prescribe, dispense or administer the drug and whether approaches to mitigate the risk are standard and well-known by the health care professional or are less familiar to the health care professional when determining whether a REMS is needed. The Agency also takes into account the health care setting(s) in which the drug is used or is likely to be used. For drugs intended for use in an outpatient setting, FDA considers the degree to which patients can be expected to reliably recognize symptoms as being associated with a drug and to take necessary actions to address adverse events. If, for example, FDA expects that a drug will likely be used in a setting where patient monitoring and certain medical equipment are not available, and believes that such measures are needed to mitigate the risks associated with the use of the drug, FDA may require a REMS with ETASU to limit use of the drug to settings in which these measures are available.

B. Expected Benefit of the Drug With Respect to the Disease or Condition

When assessing a drug's expected benefits with respect to a specific disease or condition, FDA may evaluate information about the drug's effectiveness, whether the drug treats a serious disease or condition, whether it fills an unmet medical need, and whether it can cure the disease or alleviate its symptoms. FDA may also consider the extent to which new dosage forms enhance convenience of administration and/or improve adherence to prescribed regimens, and whether new formulations or delivery mechanisms may extend treatment to patient populations who were formerly unable to use the drug.

A drug's expected benefits, however, are not considered in isolation. In determining whether a REMS is necessary, FDA's assessment of a drug's benefit is balanced against consideration of the risks associated with its use. For example, a once-a-month oral dosage form of a drug that was previously only available as a daily oral dosage form may offer a meaningful benefit in terms of convenience to the patient and adherence to medication therapy, but may have a different risk profile (e.g., a new risk associated with the new formulation, or with the longer half-life of the drug) that makes it more likely that FDA would determine that a REMS is necessary to ensure that the benefits of the drug outweigh its risks.

*Contains Nonbinding Recommendations***C. Seriousness of the Disease or Condition To Be Treated**

The seriousness of the disease or condition²⁶ to be treated is a part of FDA's overall analysis of the benefits of a drug: the more serious the disease or condition to be treated, the greater the potential benefit of the drug's measured effect in the benefit-risk assessment. Nevertheless, even for drugs intended to treat serious or life-threatening diseases or conditions, the severity, irreversibility, or duration of an associated risk may weigh in favor of a REMS. For example, if a drug indicated for long-term treatment of an indolent, asymptomatic, or slowly progressing cancer also has a more immediate risk of serious and potentially fatal cardiac arrhythmias, FDA may conclude that, without a REMS, the risk of serious cardiac arrhythmias outweighs the potential benefits of this kind of cancer treatment. In this example, a REMS may be required to educate prescribers about the risk, appropriate monitoring, and management of cardiac arrhythmias to help minimize the occurrence of the adverse event associated with the drug.

D. Whether the Drug Is a New Molecular Entity

For new molecular entities (NMEs)²⁷ and certain Biologics License Applications (BLAs) licensed under section 351(a) of the PHS Act, available information about the drug can be limited and, as a result, there may be greater uncertainty about risks associated with the use of the drug that might emerge in the post-approval setting. When available safety information about a NME or BLA indicates a serious risk, there may be uncertainties about the nature of the serious risk (e.g., the strength of the association of the adverse event with drug treatment, the likelihood of occurrence of the adverse event, or the accuracy and/or reliability of the data). Depending on the nature of the uncertainties about the risks associated with the use of the drug, FDA may require a REMS to help ensure that the benefits of the drug outweigh its risks.

²⁶ FDA has defined *serious disease or condition* as

“a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible, provided it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one.”

(21 CFR 312.300(b)); see also FDA's guidance for industry on *Expedited Programs for Serious Conditions – Drugs and Biologics*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>.

²⁷ FDA has defined the term “new molecular entity” as an active ingredient that contains no active moiety that has been previously approved by the Agency in an application submitted under section 505 of the Act (in any application approved or deemed approved from 1938 to the present), or has been previously marketed as a drug in the United States. See Manual of Policies and Procedures (MAPP) 5018.2 NDA Classification Codes, available at <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm>

*Contains Nonbinding Recommendations***E. Expected or Actual Duration of Treatment With the Drug**

The duration of treatment with a drug and the impact of treatment length on the likelihood and severity of adverse events also affect FDA's decision-making with regard to the need for a REMS. If long-term therapy with a drug appears to increase the likelihood of a serious adverse event, FDA may require a REMS either to limit the duration of treatment or to ensure that patients on long term treatment are monitored, e.g., for liver function if the drug is associated with liver toxicity.

A REMS may also be required for a drug with a relatively short duration of treatment, depending on the nature of the associated risk if, for example, the drug is associated with a serious adverse event that occurs immediately after administration. Such a REMS may require that the drug only be administered in a setting in which monitoring is available to ensure that the adverse event can be appropriately managed or in a setting in which, for example, providers have received particular risk management training. Similarly, a REMS may be required for a drug that is only intended to be administered once or twice if FDA determines that specialized training is necessary to prevent the occurrence of an adverse event associated with improper drug administration. In some cases, serious adverse events may occur even after treatment with a drug has ended. In such cases, FDA may determine that a REMS is required to ensure proper monitoring of patients for a period of time following completion of treatment.

F. Estimated Size of Population Likely To Use the Drug

In considering the estimated size of the population likely to use the drug, FDA considers, among other things, the extent to which that population includes patients expected to use the drug for unapproved uses and the risks associated with those uses. In certain cases, FDA may consider whether a REMS designed to help ensure that a drug's use is limited to its approved indications is appropriate.

VI. ADDITIONAL CONSIDERATIONS: POTENTIAL BURDEN ON THE HEALTH CARE DELIVERY SYSTEM AND PATIENT ACCESS

FDA understands that REMS, particularly those with ETASU, may impose some measure of burden on patients and/or health care providers. When considering this burden on patient access and the health care delivery system, FDA takes into account existing REMS elements for other drugs with similar risks and whether the REMS under consideration can be designed to be compatible with established medical drug distribution, procurement, and dispensing systems. FDA also considers how patients for whom the drug is indicated currently access health care (such as whether patients are in rural or medically underserved areas) and whether the REMS may impose additional access difficulties. FDA also takes into account the consequences of potential treatment interruption or delays, particularly where patients have serious or life-threatening conditions and/or have difficulty accessing health care. In such circumstances, FDA takes steps, to ensure that REMS are designed to minimize delays or interruptions in drug therapy that may have untoward clinical impact. Particularly for a REMS that requires additional procedures and controls in the patient care process, FDA also considers the characteristics,

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experience, and size of the likely prescriber population; how the drug will likely be dispensed in the setting in which it will likely be used; and the patient population likely to use the drug.

The selection of REMS elements and tools may be influenced by the extent to which they have already been used in the clinical trials to evaluate the drug's safety and efficacy, and by what is known about the effectiveness of the elements and tools more generally. Selection of risk management elements and tools is also informed by any regulatory precedent for addressing similar risks.²⁸ For example, if a serious risk is common to all members of a drug class, FDA will consider, as appropriate, how the Agency has previously managed the risk and seek opportunities to standardize the approach to managing that risk. FDA also encourages sponsors to submit REMS proposals that are compatible with established distribution, procurement, and dispensing systems. Following approval of a REMS, FDA continues to evaluate the impact of the REMS on patient access and the health care delivery system.

²⁸ In addition, the elements and tools may be driven by results of previous REMS assessments for REMS designed to address a similar risk, a similar patient population, or a similar drug distribution or dispensing system to the product under review.

EXHIBIT J



May 19, 2020

The Honorable Hector Balderas
Attorney General of New Mexico
State of New Mexico
Office of the Attorney General
P.O. Drawer 1508
Santa Fe, NM 87504

Dear Mr. Attorney General:

Thank you for your letter, addressed to the Secretary of Health and Human Services and the Commissioner of the Food and Drug Administration (FDA), regarding access to reproductive health care during the COVID-19 pandemic. The Secretary has asked me to respond to you and your 20 cosigners.

At all times, including during this pandemic, the FDA is committed to protecting the public health, so we appreciate the concerns you raised.

A copy of this letter has been sent to your cosigners.

Sincerely,

A handwritten signature in black ink, appearing to be "A. Shah", with a long horizontal stroke at the end.

Anand Shah, M.D.
Deputy Commissioner for Medical and
Scientific Affairs
Food and Drug Administration

EXHIBIT K



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SUPPLEMENT APPROVAL

Danco Laboratories, LLC

(b) (4), (b) (6)

P.O. Box 4816
New York, NY 10185

Dear (b) (4), (b) (6) :

Please refer to your supplemental new drug application (sNDA) dated and received June 22, 2022, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Mifeprex (mifepristone) Tablets, 200 mg.

This Prior Approval sNDA provides for modification to the approved single, shared system (SSS) risk evaluation and mitigation strategy (REMS) for mifepristone 200 mg tablets, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation, as well as corresponding labeling revisions to the prescribing information and the Medication Guide to align with the modification to the Mifepristone REMS Program. This SSS REMS is known as the Mifepristone REMS Program.

APPROVAL & LABELING

We have completed our review of the supplemental application, as amended. It is approved effective the date of this letter.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.¹ Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

¹ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

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Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.²

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The Mifepristone REMS Program, of which Mifeprex is a member, was originally approved on April 11, 2019, and the most recent REMS modification was approved on May 14, 2021. The Mifepristone REMS Program consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

In order to ensure the benefits of Mifeprex outweigh its risks and to minimize burden on the healthcare delivery system of complying with the REMS, we determined that you were required to make the REMS modifications outlined in our REMS Modification

² We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

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Notification letter dated December 16, 2021. In addition the following modifications were communicated during the course of the review:

- Revisions to the REMS goal to align with the updated REMS requirements.
- Replacing serial number with recording of NDC and lot number of mifepristone dispensed.
- Additional edits for clarification and consistency in the REMS Document and REMS materials (*Prescriber Agreement Forms*, *Patient Agreement Form*, and *Pharmacy Agreement Forms*).

Your proposed modified REMS, received on June 22, 2022, amended and appended to this letter, is approved. The modified REMS consists of the elements to assure safe use, implementation system, and a timetable for submission of assessments of the REMS.

The modification of the approved REMS must be fully implemented within 120 calendar days of this letter.

This shared system REMS, known as the Mifepristone REMS Program, currently includes those products listed on the FDA REMS website³.

Other products may be added in the future if additional NDAs or ANDAs are approved.

The timetable for submission of assessments of the REMS must be revised to one year from the date of the approval of the modified SSS REMS (1/3/2023) and annually thereafter.

The revised REMS assessment plan must include, but is not limited to, the following:

Program Implementation and Operations

1. REMS Certification Statistics

a. Prescribers

- i. Number of certified prescribers who have certified with the Sponsor's distributor(s) and number who have submitted *Prescriber Agreement Forms* to Certified Pharmacies
- ii. Number and percentage of newly certified prescribers
- iii. Number and percentage of active certified prescribers (i.e., who ordered mifepristone or submitted a prescription during the reporting period)

b. Pharmacies

³ <https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm>

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- i. Number of certified pharmacies
 - ii. Number and percentage of newly certified pharmacies
 - iii. Number and percentage of active certified pharmacies (i.e., that dispensed mifepristone during the reporting period)
 - c. Wholesalers/Distributors
 - i. Number of authorized wholesalers/distributors
 - ii. Number and percentage of newly authorized wholesalers/distributors
 - iii. Number and percentage of active authorized wholesalers/distributors (i.e. that shipped mifepristone during the reporting period)
2. Utilization Data
- a. Total number of tablets shipped by wholesalers/distributors, stratified by Certified Prescriber or Certified Pharmacy location
 - b. Number of prescriptions dispensed from pharmacies
3. REMS Compliance Data
- a. Audits: Summary of audit activities for each stakeholder (i.e., certified pharmacies and wholesalers/distributors) including but not limited to:
 - i. A copy of the final audit plan for each stakeholder type (provide for the current reporting period)
 - ii. The number of audits expected, and the number of audits performed
 - iii. The number and type of deficiencies noted
 - iv. For those with deficiencies noted, report the corrective and preventive actions (CAPAs) required, if any, to address the deficiencies, including the status (e.g., completed, not completed, in progress) (provide for the current reporting period)
 - v. For any stakeholders that did not complete the CAPA within the timeframe specified in the audit plan, describe actions taken (provide for the current reporting period)
 - vi. A summary report of all resulting changes to processes and procedures necessary to ensure compliance with the REMS requirements (provide for the current reporting period)
 - b. A summary report of non-compliance, associated corrective action plans (CAPAs), and the status of CAPAs including but not limited to:
 - i. A copy of the final non-compliance plans for Pharmacies and Distributors (provide for the current reporting period)
 - ii. For each instance of noncompliance below (iii-v), report the following information (provide for the current reporting period):
 - 1. A unique, anonymized ID for the stakeholder(s) associated with the non-compliance event to enable tracking over time
 - 2. The source of the non-compliance data (e.g., self-reported, audit, other)
 - 3. A root cause analysis of the non-compliance

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4. Actions to prevent future occurrences and outcomes of such actions
- iii. Prescriber compliance
 1. Number and percentage of certified prescribers who became decertified as a result of non-compliance
 - Provide a summary of reasons for decertification (provide for the current reporting period)
 2. Summary and analysis of any program deviations and corrective actions taken (provide for the current reporting period)
- iv. Pharmacy compliance
 1. Number and percentage of prescriptions dispensed that were written by prescriber(s) who did not submit a Prescriber Agreement to the dispensing Certified Pharmacy
 2. Number and percentage of mifepristone tablets dispensed by non-certified pharmacies
 3. Number and percentage of pharmacies that became decertified as a result of non-compliance
 - Provide a summary of reasons for decertification (provide for the current reporting period)
 4. An assessment of prescription delivery timelines, including percentage delivered more than four days after receipt of the prescription, duration and causes for delay. A proposal for this assessment will be submitted within 60 days of the approval of the REMS Modification.
 5. Summary and analysis of any program deviations and corrective actions taken (provide for the current reporting period)
- v. Wholesaler/distributor compliance
 1. Number of healthcare providers who successfully ordered mifepristone who were not certified
 2. Number of non-certified pharmacies that successfully ordered mifepristone
 3. Number of shipments sent to non-certified prescriber receiving locations
 4. Number of shipments sent to non-certified pharmacy receiving locations
 5. Summary and analysis of any program deviations and corrective actions taken (provide for the current reporting period)

Overall Assessment of REMS Effectiveness

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a

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proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use, as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

- a) An evaluation of how the benefit-risk profile will or will not change with the new indication;
- b) A determination of the implications of a change in the benefit-risk profile for the current REMS;
- c) *If the new indication for use introduces unexpected risks:* A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.
- d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* A statement about whether the REMS was meeting its goals at the time of that last assessment and if any modifications of the REMS have been proposed since that assessment.
- e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.
- f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including:* Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications,* provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively,

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updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted.

Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 020687 REMS ASSESSMENT METHODOLOGY

(insert concise description of content in bold capital letters, e.g.,

ASSESSMENT METHODOLOGY, PROTOCOL, SURVEY METHODOLOGIES, AUDIT PLAN, DRUG USE STUDY)

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 020687 REMS ASSESSMENT

or

**NEW SUPPLEMENT FOR NDA 020687/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION**

or

**NEW SUPPLEMENT FOR NDA 020687/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION**

or

**NEW SUPPLEMENT FOR NDA 020687/S-000/
PRIOR APPROVAL SUPPLEMENT**

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**PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING
CHANGES SUBMITTED IN SUPPLEMENT XXX**

or

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 020687/S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)**

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISIONS FOR NDA 020687

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, or website screenshots are only in PDF format, they may be submitted as such, but Word format is preferred.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, as soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in SPL format using the FDA automated drug registration and listing system (eLIST).

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

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REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call  (b) (6)

Sincerely,

{See appended electronic signature page}

 (b) (6)

Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
 - Prescribing Information
 - Medication Guide
 - REMS Document
 - Prescriber Agreement
 - Patient Agreement Form
 - Pharmacy Agreement Form

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

(b) (6)

01/03/2023 05:35:41 PM

Exhibit L

CITIZEN PETITION

April 19, 2023

The undersigned submits this petition under 21 C.F.R. § 10.30, Section 505 of the Food Drug and Cosmetic Act (21 U.S.C. § 355), and Section 7 of the Endangered Species Act of 1973 (16 U.S.C. § 1531 *et seq.*) (hereinafter, “ESA”) to request that the Commissioner of the Food and Drug Administration (“FDA”) revoke (1) the 2000 approval of the Population Council’s new drug application for mifepristone (Mifeprex® or RU-486), (2) the 2019 approval of GenBioPro, Inc.’s generic 200mg mifepristone tablet (collectively, “Mifepristone”), (3) the 2016 changes to the Mifepristone regimen and associated Risk Evaluation and Mitigation Strategy (“REMS”), (4) the 2021 changes to the Mifepristone REMS; and (5) the 2023 changes to the Mifepristone REMS in light of the FDA’s failure to comply with the requirements of the ESA when taking these actions.

Students for Life of America (“SFLA”) is the nation’s largest pro-life youth organization that uniquely represents the generation most targeted for abortion. SFLA, a 501(c)(3) charity, exists to recruit, train, and mobilize the Pro-Life Generation to abolish abortion and provide policy, legal, and community support for women and their children, born and preborn. SFLA and its members care about the environment, and its members nationwide have a vested interest in protecting the environment from pollution, protecting endangered species and habitats from destruction, and preserving these species and habitats for future generations to see and experience. SFLA seeks to prevent the dumping of Mifepristone into the waterways of the United States and the inevitable harm that has and will continue to result to endangered species.

A. Action Requested

This Petition makes one request. We request that the FDA revoke its actions to approve Mifepristone and modify the associated regimen (including the REMS) until the agency conducts the required consultation with the United States Fish and Wildlife Service (“FWS”) and National Marine Fisheries Service (“NMFS”) (collectively, “the Services”) as compelled by the ESA. Before allowing Mifepristone for human consumption, use outside of a medical setting, and disposal into the environment, the FDA must first consult with the Services to determine the extent and the effects that its Mifepristone actions have on listed endangered or threatened species or designated critical habitats in the FDA’s action area (i.e., the entire United States and its territories).

Furthermore, the undersigned’s submission of this petition is within the six-year statute of limitations applied to the Administrative Procedures Act (APA) to challenge a final agency action, in this case a challenge to a new drug approval. See *Am. Stewards of Liberty v. Dep’t of Interior*, 960 F.3d 223, 229 (5th Cir. 2020), *cert. denied sub nom. Yearwood v. Dep’t of the Interior*, 141 S. Ct. 1062 (2021) ([APA challenges] must be brought within six years of the final agency action allegedly causing a plaintiff’s injury).¹ Most recently, FDA’s 2021 and 2023 modification to the

¹ See *Bennett v. Spear*, 520 U.S. 154 at 175 (1997) (holding that under § 7 of the ESA, claims can be brought pursuant to the APA). “Although the APA itself contains no specific statute of limitations, a general six-year civil action statute of limitation applies to challenges under the APA. 28 U.S.C. § 2401(a)” (“[E]very civil action commenced against the United States shall be barred unless the complaint is filed within six years after the right of

Mifepristone REMS to formally end the requirement of in-person dispensing and approving the over-the-counter sale of Mifepristone re-opened the period by which interested parties may challenge FDA's decision to approve Mifepristone.² According to the D.C. Circuit Court of Appeals, when an agency either implicitly or explicitly alters its former decision, the period during which it may be challenged is likewise "altered" to begin again.³

B. Statement of Grounds

The FDA has a legal obligation to comply with the ESA. As set forth in this citizen petition, the FDA's actions on Mifepristone have failed to meet the requirements of the ESA and, therefore, must be revoked until the agency can implement measures to ensure that its actions do not adversely affect listed endangered or threatened species or designated critical habitats. Failure to do so could lead to the extinction of these species.

1. The FDA's Actions on Mifepristone and Failure to Comply with the ESA

a. The 2000 Approval of Mifepristone

When the FDA approved Mifepristone in 2000 to be used for chemical abortions, the agency did not consult the Services to determine the effects of Mifepristone on listed endangered or threatened species or designated critical habitats. The FDA merely relied on an environmental assessment that the Population Council performed under the National Environmental Policy Act.

In a document entitled, "ENVIRONMENTAL ASSESSMENT AND FINDING OF NOT SIGNIFICANT IMPACT FOR NDA 20-687 MIFEPRISTONE TABLETS," the FDA stated without further explanation that "[a]dverse effects are not anticipated upon endangered or threatened species." This conclusion runs afoul of the requirements of the ESA.

This conclusion also made numerous incorrect assumptions about how Mifepristone could enter the environment. Indeed, the FDA did not conduct an environmental study regarding the potential impact Mifepristone could have on the nation's wastewater. The problem with the FDA's assessment is that it only reviewed the impact that packaging, partially empty packaging, production waste, and pharmaceutical waste would have on the environment, and underestimated the impact the excretion of Mifepristone would have on the environment.⁴ Further, it underestimated the number of chemical abortions, which are abortions committed through use of Mifepristone.

action first accrues."); *Sierra Club v. Penfold*, 857 F.2d 1307, 1315 (9th Cir.1988) (holding that § 2401(a) applies to the APA). *Turtle Island Restoration Network v. U.S. Dep't of Com.*, 438 F.3d 937, 942–43 (9th Cir. 2006).

² Under the re-opener doctrine, the 2019 establishment of a shared REMS program between the generic Mifeprex® and Mifepristone would have also provided a timely window by which a party may have filed a petition requesting FDA revisit the approval of Mifepristone related to ESA § 7(a) consultation.

³ "The reopener doctrine allows an otherwise untimely challenge to proceed 'where an agency has—either explicitly or implicitly—undertaken to reexamine its former choice.'" *Nat'l Biodiesel Bd. v. EPA*, 843 F.3d 1010, 1017 (D.C. Cir. 2016) (quoting *Nat'l Mining Ass'n v. U.S. Dept. of Interior*, 70 F.3d 1345, 1351 (D.C. Cir. 1995)).

⁴ 1996 Environmental Assessment and/or FONSI Application Number 20-687 page 1 of Cover Letter.

b. The 2016, 2019, 2021, and 2023 Changes to the Mifepristone Regimen and REMS

When the FDA made significant changes to the Mifepristone regimen and REMS in 2016, 2019, 2021, and 2023, the agency simply failed to conduct any ESA consultation or environmental assessment. This failure flies in the face of the ESA and must be corrected immediately—especially in light of the FDA’s removal of the in-person dispensing requirement, which opened up the floodgates to do-it-yourself abortions at home and disposal of Mifepristone directly into our nation’s water supply.

2. The Legally Necessary Consultation with the Services Regarding the Impact of Mifepristone on Listed Endangered or Threatened Species or Designated Critical Habitats

The purpose of the ESA is to provide a means to conserve the ecosystems upon which endangered and threatened species depend and provide a program for the conservation of such species. Section 7 of the ESA, codified at 16 U.S.C. § 1536 (“Section 7”), directs all Federal agencies to participate in conserving these species. Specifically, Section 7(a)(1) of the ESA charges Federal agencies to aid in the conservation of listed species, and Section 7(a)(2) requires all federal agencies cooperate and consult with the Services to aid in the conservation of listed species and ensure that their activities are not likely to jeopardize the continued existence of federally listed species or destroy or adversely modify designed critical habitats.

First, in order to ensure compliance with the ESA, before taking action such as approving a drug or medication, a federal agency such as the FDA must first define the action area and submit a proposed list of impacted species or request from the Services a list of impacted species. The purpose of this is to encompass all listed species that may be impacted by the proposed agency action. The species list must include all listed and proposed species and designated critical habitats that may be present in the action area. The action area must not neglect indirect effects, such as stormwater run-off, or the effect felt in wastewater or wastewater effluent and the route it takes to public waterways. And because there are no geographical limitations to the FDA’s approval of mifepristone, the relevant action area is the entire United States and its territories.

Second, the FDA must determine whether the proposed action *may affect* a Section 7 resource, or a species on the aforementioned list. This is done through assessments of the direct or indirect effects mentioned previously.⁵ Every listed species or habitat must be analyzed through this lens. As discussed below, the “may affect” designation is a low bar. And given the nationwide action area and known potential effects of Mifepristone, a “no effect” determination cannot apply to the FDA’s actions on Mifepristone. The “no effect” determination applies only in very limited circumstances, such as when the species ranges and critical habitat do not overlap with the action area.

Third, if the proposed action *may affect* a Section 7 resource, the FDA must enter into “information consultation” with the Services to analyze the aforementioned potential direct and

⁵ Direct effects are those that are caused by the action, while indirect effects are those that are caused by the action and are later in time, but still are reasonably certain to occur.

indirect, adverse, and beneficial effects of the action on the Section 7 resources that may be affected. The ESA requires clear documentation (i.e., a Biological Assessment or Biological Evaluation) that there is a determination being made, regardless of the effect itself. And the Services must expressly concur in writing with any determination that the action is not likely to adversely affect any Section 7 resources.

Finally, in instances where an adverse effect is *likely*, the ESA requires a “formal consultation” between the FDA and the Services wherein the FDA would submit further documentation to the Services and provide a full Biological Opinion on the impact, in this case of Mifepristone, would have on any listed species or habitats. Beyond this, the FDA would be required to show Mifepristone would not jeopardize, destroy, or adversely affect listed species or habitats, and if it does, then either seek an exemption or provide for reasonable and prudent alternatives.

3. The Section 7 Regulations and Federal Case Law on ESA Consultations

Section 7 consultation requirements apply to federal agency actions, including actions on federal land and actions on private land with a federal nexus. The Services’ joint regulations⁶ on Section 7 consultations define an agency action as all activities or programs of any kind authorized, funded, or carried out, in whole or in part, by Federal agencies in the United States or upon the high seas. Examples include, but are not limited to:

- (a) actions intended to conserve listed species or their habitat;
- (b) **the promulgation of regulations;**
- (c) **the granting of licenses,** contracts, leases, easements, rights-of-way, **permits,** or grants-in-aid; or
- (d) actions directly or indirectly causing modifications to the land, water, or air.

50 C.F.R. § 402.02 defines an “action” as anything that “includes any activity authorized, funded, or carried out by a federal agency, including permits and licenses.” Federal courts have interpreted an agency action requiring consultation in the context of the ESA to be a low threshold, lower than that of other Federal environmental protection statutes, including the National Environmental Policy Act (NEPA):

It is instructive to compare the requirements under the ESA to those under NEPA. Whereas NEPA asks the agency to identify and prepare an environmental impact report for “significant” impacts on any aspect of the environment, the ESA requirements are triggered by a lower threshold, but for a narrower set of impacts. The agency must identify *any* potential effect, however small, on listed species and consult with the relevant agencies about the proposed action. *See Karuk Tribe of California v. U.S. Forest Service*, 681 F.3d 1006, 1027 (9th Cir. 2012).

Inst. for Fisheries Res. v. United States Food & Drug Admin., 499 F. Supp. 3d 657, 668 (N.D. Cal. 2020). Similarly, the D.C. Circuit found in 2021 that:

⁶ 50 C.F.R. § 402 *et seq.*

Implementing regulations promulgated pursuant to the Endangered Species Act require an agency to “determine whether any action **may affect** listed species or critical habitat,” and, if so, to **consult with the Services**. 50 C.F.R. § 402.14(a); *see* 16 U.S.C. § 1536(a)(2). Only if an agency determines that its action will have no effect on listed species or critical habitat can it dispense with consultation. *Ctr. for Biological Diversity v. U.S. Dep’t of Interior*, 563 F.3d 466, 475 (D.C. Cir. 2009). “May affect” purposefully sets a low bar: **“Any possible effect, whether beneficial, benign, adverse or of an undetermined character, triggers the formal consultation requirement.”** *Interagency Cooperation—Endangered Species of 1973, as Amended*, 51 Fed. Reg. 19,926, 19,949 (June 3, 1986). “Thus, actions that have any chance of affecting listed species or critical habitat — even if it is later determined that the actions are ‘not likely’ to do so — require at least some consultation under the ESA.” *Karuk Tribe of Cal. v. U.S. Forest Serv.*, 681 F.3d 1006, 1027 (9th Cir. 2012).

Growth Energy v. Env’t Prot. Agency, 5 F.4th 1, 30 (D.C. Cir. 2021) (emphasis added). Likewise, the ESA broadly defines “take” to include a wide range of actions, such as to harass, harm, pursue, hunt, shoot, wound, kill, trap, capture, or collect an endangered wildlife species, or any attempt to engage in such conduct. 16 U.S.C. § 1532(19). The Northern District of California has stated that “mere harm” to a listed species can constitute a take for the purposes of the Act. What this means is that an action Agency proceeding without guidance from the Services puts itself at great risk for the substantial civil or criminal liabilities enumerated in the Act in the event their action harms an endangered species or listed habitat. *See Pacificans for a Scenic Coast v. California Dep’t of Transportation*, 204 F. Supp. 3d 1075 (N.D. Cal. 2016). In the above referenced *Karuk* case, the Ninth Circuit in explaining that the definition of agency “action” can cover a variety of activities found that:

[t]here is “little doubt” that Congress intended agency action to have a broad definition in the ESA, and we have followed the Supreme Court’s lead by interpreting its plain meaning “in conformance with Congress’s clear intent.” *Pac. Rivers Council v. Thomas*, 30 F.3d 1050, 1054–55 (9th Cir.1994) (citing *Tenn. Valley Auth.*, 437 U.S. at 173, 98 S.Ct. 2279).

The ESA implementing regulations limit Section 7’s application to “‘actions in which there is discretionary Federal involvement or control.’” *Nat’l Ass’n of Home Builders v. Defenders of Wildlife*, 551 U.S. 644, 666, 127 S.Ct. 2518, 168 L.Ed.2d 467 (2007) (quoting 50 C.F.R. § 402.03). The Supreme Court explained that this limitation harmonizes the ESA consultation requirement with other statutory mandates that leave an agency no discretion to consider the protection of listed species. *Home Builders*, 551 U.S. at 665–66, 127 S.Ct. 2518.

Karuk at 1020–21 (9th Cir. 2012). It is clear that many courts have established that under the ESA, “agency action” is both a low bar that an agency will very likely cross but also a broad one. “Any

possible effect” triggers the FDA’s duty to consult with the Services; and there is no doubt that Mifepristone has “any possible effect” on an endangered species.

Federal courts define the requirements of Section 7 as a two-fold burden. The first is a procedural burden: the action agency is to engage in consultation with the Services as the experts in the field, and the second is a more substantive requirement: to ensure that the proposed action will not jeopardize a listed species or its critical habitat.

At the onset, the action agency and Services engage in “informal consultation.” Informal consultation is a wide-ranging term, and generally covers the conversations, correspondence, and discussions between the Services and action agency at the early stages to see whether or not the next step is necessary – formal consultation, as oftentimes the two parties can determine then and there that there will be no impact on a listed species or habitat. In the event the proposed action requires “formal” consultation, the first step in this process is to form a “biological assessment” followed by a biological opinion from the Services. This opinion summarizes the information needed to show the potential impact the agency action might have. Only at this point, if the action will not jeopardize an endangered species or habitat, may the action agency proceed. If there is a chance of endangerment, the Services will provide “reasonable and prudent” alternatives, and the action agency is encouraged to adopt those alternatives, or risk civil and criminal penalties for failing to comply with the ESA. *See Pacificans* generally, 204 F. Supp. 3d 1075 (N.D. Cal. 2016).

The purpose of Section 7’s consultation provision is to determine if any agency may adversely affect an endangered species or habitat. By failing to conduct even an informal consultation, the FDA did not ensure that the approval of Mifepristone would not harm potential listed species.

The purpose of the consultations is to “draw on the expertise of ‘wildlife agencies to determine whether [an] action is likely to jeopardize a listed species’ or its habitat, and ‘to identify reasonable and prudent alternatives’ to avoid those harmful impacts.” *Ctr. for Biological Diversity*, 847 F.3d at 1075 (quoting *Karuk Tribe*, 681 F.3d at 1020). NMFS provides consultation on actions involving marine and anadromous species and habitats, and FWS for all other species and habitats.

Ecological Rts. Found. v. Fed. Emergency Mgmt. Agency, 384 F. Supp. 3d 1111, 1115 (N.D. Cal. 2019). The consultation process need not proceed to the formal stage, if as in the case of *Shafer*, the action agency and the wildlife agency agree it is not necessary:

While the consultation process can take a variety of forms, the action agency often performs a preliminary review to determine whether the proposed action could affect any listed species. *See* 50 C.F.R. § 402.14(a); *see also* 16 U.S.C. § 1536(c); 50 C.F.R. §§ 402.10–402.13. If the action agency determines—and the wildlife agency concurs—that no listed species or critical habitats are likely to be adversely affected, then no formal consultation is required. 50 C.F.R. § 402.14(b)(1). But if either the action agency or the wildlife agency concludes that the proposed action “may affect” a listed species or its critical habitat, then a formal consultation

begins. *Id.* § 402.14(a).

Shafer & Freeman Lakes Env't Conservation Corp. v. FERC, 992 F.3d 1071, 1079 (D.C. Cir. 2021). The case law is clear that not every time there is an agency action will there be even a formal consultation, but in failing to even begin the informal process, the FDA failed to comply with a Congressional mandate placed upon all federal agencies.

Federal courts have interpreted the triggering of ESA's Section 7 protections to be a low bar, lower than similar federal statutory constructs, but that the Act's mandate to protect endangered species and threatened habitats do require action agencies that propose new actions to consult in some degree with the relevant Service. In approving Mifepristone, the FDA bypassed this requirement. This citizen petition requests that the FDA comply with the ESA and conduct the appropriate consultation with the Services.

4. Examples of Endangered Species Potentially Affected by the FDA's Actions

The current list of endangered species recognized by the Services contains nearly 1,500 different species and can be found at <https://ecos.fws.gov/ecp0/reports/ad-hoc-species-report?kingdom=V&kingdom=I&status=E&status=T&status=EmE&status=EmT&status=EXPE&status=EXPN&status=SAE&status=SAT&mapstatus=3&fcritab=on&fstatus=on&fspecrule=on&finvpop=on&fgroup=on&header=Listed+Animals>.

By way of some specific examples, *Canis rufus*⁷ (more commonly known as the red wolf) is a canine native to the Southeastern United States, intermediate in size between the grey wolf and coyote. Originally listed in 1967 under the Endangered Species Preservation Act of 1966 (the predecessor act to the ESA) the red wolf is critically endangered with fewer than 50 currently in the wild, and around 200 in captivity. The red wolf is gradually being reintroduced into the Southeastern United States, and often inhabits wetlands, forest, and some agricultural lands. The red wolf is at one of the more sensitive stages of reintroduction into these ecosystems. Similarly,



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*Lepidochelys kempii*⁸, or Kemp's ridley sea turtle, listed since 1970, is the world's rarest and most endangered species of sea turtle, finds its range along the Gulf Coast region of the Southeastern United States, and often employs the coasts of Texas as a primary nesting range. The Kemp's ridley sea turtle numbers fewer than 10,000 and faces critical habitat loss from human impact on the Gulf of Mexico. *Percina pantherine*⁹, or leopard darter, is a freshwater fish originally found throughout Oklahoma and Arkansas, and listed as an endangered species since 1978. The leopard darter's habitat throughout these states is often connected to outflows from sewage processing plants and other human elements that can cause disruption. *Gymnogyps californianus*¹⁰, the California condor, is another listed species within the United States that has a long history of conservation having being listed since 1967 (similar to the red wolf above). According to the Fish and Wildlife Service, over \$35 million has been spent on California condor conservation efforts, making it one of the most expensive conservation projects in American history.¹¹ With fewer than



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¹¹ <https://web.archive.org/web/20070808215527/http://www.fws.gov/hoppermountain/cacondor/FAQ.html#money>

600 living, in captivity and the wild, it remains one of the world's rarest bird species. Originally inhabiting locations across North America, today in the wild they can only be found in small portions of Southern California. California condor feed off of a variety of carrion across their habitat in Southern California, and will consume nearly any non-bird carcass they come across, including aquatic creatures. *Crocodylus acutus*¹², the American crocodile, inhabits portions of southern Florida as well as locations across the Caribbean and parts of South America. Its status as a member of the endangered species list is owed to 20th Century over-hunting and destruction of their habitats by human actions. There are fewer than 2,000 members living in Florida; they feed on many aquatic creatures and can inhabit nearly any fresh or salt-water environment within the southern portion of that state. Finally, *Oncorhynchus nerka*¹³, the sockeye salmon, is one of the most popular salmon used for food, and is a listed species in locations within the United States. Compared to soho salmon, steelhead trout, and Chinook salmon, populations of sockeye in the Pacific Northwest are not experiencing a resurgence in population.¹⁴ In fact, populations in Idaho and Oregon have become completely extinct. In recent years populations across North America have come under their spawning estimates and are at 50-year lows in some places. Sockeye inhabit many fresh and saltwater locations across the Pacific Northwest and Alaska and are heavily impacted by human activity in those waters.

All of these listed species depend on a variety of ecosystems within the United States that are often impacted by human activity. SFLA and its members are concerned that the failure of the FDA to conduct consultation with the Services has led to irreparable harm to many listed species and habitats and will likely lead to the destruction of some of these species. When federal agencies propose actions that could impact these ecosystems, they are required to consult with the Services to determine if these actions will harm these three species, among the list of nearly 1,500 individual species. FDA did not do this when approving Mifepristone in 2000 and changing the regimen in 2016, 2019, 2021, and 2023.



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¹⁴ <https://www.wsj.com/articles/SB10001424052748703657604575005562712284770>

The FDA Did Not Conduct Sufficient Advanced Studies on the Impact Mifepristone Could Have on the Nation's Water Supply at Any Point Before or Since Formal Approval of Mifepristone for Women and Girls in 2000. This Can Have a Negative Impact on Endangered Species and Threatened Habitats.

The FDA did not conduct sufficient advanced studies on the impact Mifepristone could have on the nation's water supply when the Mifepristone regimen was approved for women and girls in 2000. In the lead up to 2000 approval, the FDA reported that there would be high standards for disposal related to Mifepristone.¹⁵ This has not been the case.

Mifepristone and fetal remains in wastewater have impacts beyond humans and onto animals and plants. Mifepristone usage results in the generation of Medical Waste¹⁶ and must be treated as such. The residual effects of exposure to Mifepristone in the nation's waterways can impact animals, causing teratologic repercussions or congenital anomalies like birth defects to animals.¹⁷ Proper control of drugs, hormones, and chemicals in wastewater is vital to human health and the health of other life exposed.

a. The FDA did not conduct sufficient advanced studies on the impact Mifepristone could have on the nation's water supply when the Mifepristone regimen was approved for women and girls in 2000.

The FDA did not conduct sufficient advanced studies on the impact Mifepristone could have on the nation's water supply when the Mifepristone regimen was approved for women and girls in 2000. This has resulted in an incalculable amount of human remains and drug residue entering our nation's water supply following the usage of Mifepristone. This has not been analyzed from the perspective of the Endangered Species Act and the effect of Mifepristone on listed species or habitats. From the 1996 report that the FDA prepared for Mifepristone's approval:

The Food and Drug Administration, Center for Drug Evaluation and Research (CDER) has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared. In support of their new drug application for Mifepristone Tablets, The Population Council has prepared an environmental assessment in accordance with 21 CFR 25.3a (attached) which evaluates the potential environmental impacts of the manufacturer, use and disposal of the product. Mifepristone is a synthetic drug which will be administered orally to provide a medical approach to the termination of early pregnancy. Mifepristone may enter the environment from the excretion by patients, from disposal of pharmaceutical waste or from emissions from manufacturing sites. . . . The Center for Drug Evaluation and Research has concluded

¹⁵ 1996 Environmental Assessment and/or FONSI Application Number 20-687 page 02.

¹⁶ Medical waste, as defined by the EPA: "Generally, medical waste is healthcare waste that [] may be contaminated by blood, body fluids or other potentially infectious materials and is often referred to as regulated medical waste."

¹⁷ Gonsioroski A, Mourikes VE, Flaws JA. *Endocrine Disruptors in Water and Their Effects on the Reproductive System*. Int J Mol Sci. 2020 Mar 12;21(6):1929. doi: 10.3390/ijms21061929. PMID: 32178293; PMCID: PMC7139484.

that the product can be manufactured, used, and disposed of without any expected adverse environmental effects.¹⁸

By their own admission, the FDA failed to study or assess the environmental impact of Mifepristone itself, but also the natural “by-product” of Mifepristone use: medical and pathological waste. The study only evaluated the impact of “manufacturer, use and disposal of the product,” i.e., the impact of trash from the packaging. There was not any evaluation of Mifepristone’s effect on the water supply or pollution for the people or animals who consume that water.

i. In the lead up to 2000 approval, the FDA reported that there would be high standards for disposal related to Mifepristone. This has not been the case.

The 1996 Environmental Assessment stated that there would be high standards for disposal; however, the focus was primarily on the drug itself and its associated packaging, not the chemical remnants, human remains, and other tissues which are a natural result of Mifepristone usage. This waste is generally flushed into the wastewater system. Proliferation of Mifepristone usage is only increasing with the 2016 changes to the REMS, the 2021 removal of the in-person dispensing requirement, and the authorization of mail-order pills; thus, the associated pollution into the waterways is growing.

When Mifepristone was first approved by the FDA in 2000, the Environmental Assessment prepared for the FDA included specific provisions for disposal locations. That assessment required that clinics or healthcare providers prescribing Mifepristone to follow the Center for Disease Control guidelines for handling hazardous waste. Specifically, it stated that “the applicant will use a licensed incineration or grinding and landfill facility to dispose of this type of material.”¹⁹ However, considering the purported “convenience” afforded by the usage of Mifepristone (compared to the clinical setting), the majority of abortions via Mifepristone are occurring in the home. In fact, it is often touted as one of the main benefits of Mifepristone, as explained by the Guttmacher Institute: “[m]edication abortion can be completed outside of a medical setting—for example, in the comfort and privacy of one’s home.”²⁰

More than half of all abortions (54%) are committed with Mifepristone.²¹ This figure is an estimate, as the actual percentage of abortions as committed by Mifepristone is unknown as there is no national abortion reporting law.²² States don’t report uniformly, and some report nothing at all. This is exacerbated by the chaos of online purchases, and the fact that many Mifepristone²³ pill vendors are located internationally. Given current trends, Mifepristone may soon cause more than 90% of all abortions. Three-quarters of abortions in Europe are committed with Mifepristone pills, according to *the New York Times*.²⁴ And it can be more, as an NIH report notes that countries like

¹⁸ 1996 Environmental Assessment and/or FONSI Application Number 20-687 page 1 of Cover Letter.

¹⁹ 1996 Environmental Assessment and/or FONSI Application Number 20-687 page 3.

²⁰ <https://www.guttmacher.org/article/2022/02/medication-abortion-now-accounts-more-half-all-us-abortions>

²¹ *Id.*

²² https://papers.ssrn.com/sol3/papers.cfm?abstract_id=2306667

²³ Some studies refer to Mifepristone and misoprostol usage generally as “Chemical Abortion.”

²⁴ <https://www.nytimes.com/2022/05/09/upshot/abortion-pills-medication-roe-v-wade.html>

Finland use Mifepristone pills 97.7% of the time, and in Sweden, the pills are used more than 96.4%.²⁵ The number of fetal remains flushed into the wastewater system is only increasing and it is likely that the United State will be following Europe's lead in light of the United States Supreme Court's overturning of *Roe v. Wade* and increasing restrictions on chemical abortions in many states.

The industry's practice to date is to allow the byproducts of Mifepristone usage to be flushed into the patient's toilet, as is FDA's; but everything that is flushed goes into America's wastewater system.²⁶ Most Americans know that the only things you can safely flush are the "three Ps": Pee, Poo, Paper.²⁷ In fact, "the U.S. Environmental Protection Agency is encouraging all Americans to only flush toilet paper."²⁸ The EPA is very direct on how to "protect local waterways" by not flushing the wrong things.²⁹ Treated wastewater is released into local waterways where it's used again for any number of purposes, such as supplying drinking water, irrigating crops, and sustaining aquatic life.³⁰

The route by which human waste travels from bathrooms and into the waterways is an important reference point to highlight the route by which pharmaceuticals follow the same path, and namely the manner by which Mifepristone remnants can harm endangered species. Oftentimes what is in human waste and uterine content contains specific chemical compounds that find their way back into water; whether that be drinking water, groundwater, or surface water. Those compounds break down into their various member parts, either through human filtering, or through chemical processes. These "metabolites", can be either "active" or "inactive." Active pharmaceutical metabolites can still carry out the intention of the original drug or chemical compound they were a part of, even after consumption by humans. Thus, in cases where metabolites of the drug or compound are active, once it cycles through the liver it can still work in the body (or other bodies) to facilitate the action the chemical or drug was designed to do. Mifepristone itself has several active metabolites that are still functioning as intended even after filtration by the human body and expulsion from the uterus.³¹ These metabolites can be found in uterine contents like placenta and fetal remains, as well as urine or feces; these naturally find their way into the wastewater system. In fact, the directly expelled uterine contents are far more chemically tainted than waste would be, as those materials are directly passed into the water system because of Mifepristone and are not just byproducts passed off in waste.

Many studies have been conducted on the effects pharmaceutical metabolites can have after they are secreted by the body and end up in water, or in agricultural and industrial settings where metabolites end up in runoff, to see to what extent and degree their original purpose still survives.

³² Pharmaceutical metabolites of chemicals can end up in a wide range of water sources, after

²⁵ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8567957/>

²⁶ <https://cwhccolorado.com/services/medication-abortion/aftercare-medication-abortion/index.html>

²⁷ <https://www.portland.gov/bes/safe-flush>

²⁸ <https://www.epa.gov/newsreleases/epa-encourages-americans-only-flush-toilet-paper>

²⁹ https://www3.epa.gov/npdes/pubs/centralized_brochure.pdf

³⁰ <https://www.cwea.org/news/epa-bans-flushing-all-drugs-including-hazardous-waste-drugs/>

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<https://pubmed.ncbi.nlm.nih.gov/14698071/#:~:text=The%20three%20most%20proximal%20metabolites,human%20progesterone%20and%20glucocorticoid%20receptors>

³² <https://setac.onlinelibrary.wiley.com/doi/pdf/10.1897/09-173.1>

either human consumption or other human activities such as the application of herbicides, pesticides, and fungicides. In more recent studies of the impact pharmaceuticals have had on the environment shows that wastewater treatment plants (WWTPs) are unable to entirely treat the water and remove the active metabolites from human waste and by extension human uterine content that ends up in the water. What this in turn means is that through human consumption and transmission into waste, many potentially harmful pharmaceuticals are finding their way into our waterways. Wastewater, once it is treated at the WWTP and sent back into the environment in the form of effluent, could very likely still contain the active metabolites of whatever drugs were filtered into it by humans along the way. The FDA and EPA do not attach other regulation on the amount of potentially harmful chemicals that enter our waterways. The FDA in approving Mifepristone did not determine whether the amount of that drug that enters our waterways was enough to harm endangered species. The FDA failed to comply with Section 7 by approving Mifepristone despite not knowing the full impact of its active metabolites. These same metabolites that enter the wastewater system and eventually the environment where it likely effects endangered species.

Medications and chemicals flushed into the wastewater system cause particular problems.³³ Yet this is permissible because of the FDA's failure to comply with Section 7 of the ESA. There has been no comprehensive review of the effect this widespread proliferation of Mifepristone, and its consequences, could have on American water, and thereafter plants and animal life. The 1996 Environmental Assessment laid out specific instructions for the proper disposal methods to be used with Mifepristone packaging, but the study failed to consider how to properly dispose of the results of Mifepristone use itself.

Surgically extracted fetal remains, and chemically expelled fetal remains, tissues, and fluids are treated differently; including how they are disposed of. Many state laws exist that elucidate the proper disposal method for fetal and human remains in the context of surgical abortion in order to protect public health.³⁴ Many of these state laws provide that fetal remains are to be cremated or properly buried, and in fact Vermont's law states:

Fetal remains shall be disposed of by burial or cremation unless released to an educational institution for scientific purposes or disposed of by the hospital or as directed by the attending physician in a manner which will not create a public health hazard. Permission shall be obtained from one of the parents, if competent, for disposition in all cases where a funeral director is not involved. One copy of the fetal death report shall be printed in such manner that completion and signing by the physician or medical examiner shall constitute permission to make final disposition of the fetal remains.³⁵

These laws contemplate surgical abortion only, and have not kept up with the pace of Mifepristone usage. It's clear the same concern applies in the case of chemical abortion. It is antithetical to the passage of these laws or similar laws to allow the products of Mifepristone usage

³³ <https://www.epa.gov/sites/default/files/2015-06/documents/how-to-dispose-medicines.pdf>

³⁴ See Fla Admin. Code 59A-9.030, Ga Code Ann. § 16-12-141.1(a)(1), Miss Code Ann. § 41-39-1, Or Rev. Stat. § 432.317(3), Ohio Admin. Code § 3701-47-05(A), Ariz Rev. Stat. 36-331, and Tenn Code Ann. § 68-3-506.

³⁵ 18 VT Stat. Ann. § 5224(a).

to be transmitted into the waterways when surgically aborted fetuses are properly disposed of through cremation or burial.

Unfortunately, this same level of concern has not been extended to usage of Mifepristone, despite the fact that chemical abortion caused by Mifepristone creates more harmful byproducts, along with the expected fetal remains, because it includes the remains of Mifepristone itself. Other state laws provide that citizens have a right to know what, if any, contaminants are in their water. Plus, a state's waterways are highly regulated in general.³⁶ This same level of regulation should be extended to chemical pollutants in our waterways. Further, the FDA must comply with Section 7's requirements of consultation with the Services to determine the effects of this medical waste on listed species or habitats in our nation's waters.

b. Mifepristone remains and fetal remains in wastewater have impacts beyond humans and onto animals and plants. Mifepristone usage results in the generation of Medical Waste and must be treated as such.

Mifepristone and fetal remains in wastewater have impacts beyond humans and onto animals and plants. The EPA acknowledges that pharmaceuticals and human remains can impact the fertility of animals and fish.³⁷ Mifepristone in wastewater is distinct from a natural spontaneous miscarriage, as the products of Mifepristone are chemically tainted with this drug. As Students for Life of America President Kristan Hawkins noted in a 2020 letter to then FDA Commissioner Stephen Hahn, a re-evaluation of the environmental impact of the volume of human remains is needed, given the current status. Hawkins wrote:

During the approval process for RU-486, an environmental impact study for the drugs focused on the impact of packaging for the drugs, rather than on the impact of human remains in our wastewater system and ground water. Today, with so many lives ending by such chemical abortion pills, it's vital to reopen an inquiry into the environmental impact on our water and land as so many human beings are being flushed away. When you consider that the Environmental Protection Agency recommends against flushing tampons to preserve the environment and water safety, how much more significant is disposing of human remains through the wastewater systems across America?³⁸

The need to protect and preserve endangered species and habitats, among other environmental priorities, impacts everyone. This led the Federal Government to create agencies such as the EPA and the Services and to pass legislation such as the Endangered Species Act and Clean Water Act. However, as the EPA notes, states lead the way and there is not much that the EPA can do in the realm of Medical Waste. The "EPA has not had authority, specifically [to regulate] medical waste, since the Medical Waste Tracking Act (MWTa) of 1988 expired in 1991."³⁹ In fact, the EPA encourages citizens "to contact your state environmental program first when disposing of medical waste" and "[c]ontact your state environmental protection agency and

³⁶ See Fla Stat 403.021(2), (10).

³⁷ https://cfpub.epa.gov/si/si_public_record_report.cfm?dirEntryId=312892&Lab=NHEERL

³⁸ <https://www.epa.gov/newsreleases/epa-encourages-americans-only-flush-toilet-paper>

³⁹ <https://www.epa.gov/rcra/medical-waste#who%20regulates%20medical%20waste>

your state health agency for more information regarding your state's regulations on medical waste.”⁴⁰ Rather than tackle the byproducts of Mifepristone after they have already entered our waterways, this Citizen Petition suggests to the FDA that they must handle the problem at the beginning. The FDA must determine the impact that Mifepristone may have on listed species or habitats through consultation with the Services, and thus learn of the impact of these chemical byproducts on our ecosystems and waterways.

Given that no complete Environmental Impact Study took place in 1996, the true impact of Mifepristone, human tissues, and human remains on our nation's wastewater system is largely unknown. It is likely that the nation's drinking water is contaminated in some appreciable amount by the increasing abundance of Mifepristone and human remains – as of February 2022, 54% of all abortions were performed via Mifepristone usage, up from 39% in 2017 – being flushed into the system.^{41 42} This can have detrimental effects on the fertility of animals, as well as having unknown detrimental effects on plant life and ecosystems. As was stated above, this is only going to increase in the coming months and years as Mifepristone use becomes the primary method of abortion in the United States.

Human remains are considered “pathological waste,” which the World Health Organization (WHO) recommends being carefully treated by incineration or other special handling.⁴³ Mishandling human remains and Medical Waste can lead to severe consequences. Those negative consequences can impact animals, plants, and people. As the WHO notes: “[t]he disposal of untreated health care wastes in landfills can lead to the contamination of drinking, surface, and ground waters if those landfills are not properly constructed.”⁴⁴ The American Academy of Family Physicians, in discussing Medical Waste disposal in non-medical locations, notes:

[h]ome based health care can create medical waste which can be hazardous if not disposed properly. Inappropriate medical waste disposal can pose harmful environmental concerns and significant health risks to the public, which include but are not limited to, potential water contamination, ... and toxic exposure to pharmaceutical products. The AAFP encourages practices to keep all medical and non-medical waste separate to avoid contamination and to facilitate safe disposal of all medical waste. The importance of routine medical waste disposal and destruction practices should be stressed at all city and county levels of collection.⁴⁵

Due to the FDA's failure to conduct proper consultation with the Services in the context of the Endangered Species Act, it is unknowable the impact of this pathological waste may have on listed species or habitats. Even if unknowable, it is very likely to cross the low threshold for agency actions enumerated above by federal courts to constitute a take against the ESA. This must be remedied through FDA complying with Section 7's requirements and consultation with the Services.

⁴⁰ <https://www.epa.gov/rcra/medical-waste#who%20regulates%20medical%20waste>

⁴¹ <https://www.guttmacher.org/article/2022/02/medication-abortion-now-accounts-more-half-all-us-abortions>

⁴² <https://all.org/abortion/abortion-statistics>

⁴³ <https://www.who.int/news-room/fact-sheets/detail/health-care-waste>

⁴⁴ <https://www.who.int/news-room/fact-sheets/detail/health-care-waste>

⁴⁵ <https://www.aafp.org/about/policies/all/medical-waste-disposal.html>

i. The residual effects of exposure to Mifepristone in the nation's waterways can impact animals, causing teratologic repercussions and congenital anomalies like birth defects, to animals.

In the FDA's 1996 Environmental Assessment, the Teratogenicity realities of Mifepristone pills were shown to impact rats, mice, and rabbits in testing. As a Harvard University paper, *The Life of the Abortion Pill in the United States*, states, initial studies of the drugs included requirements that the women agree to a surgical abortion if Mifepristone failed because of the risk of birth defects.⁴⁶ This way, the products of surgical abortion would be disposed through healthcare facility disposal systems, rather than getting flushed into waterways.

The report noted:

[a]nimal toxicology on both mifepristone and misoprostol show teratologic effects in animals, and usually such teratologic effects in animals will translate or have a high possibility of translating to teratologic effects in humans. Dr. Bardin, an endocrinologist and independent consultant for the Population Council, reported at a 1996 FDA Advisory Committee meeting, that 21 children have been born to women who changed their minds, after mifepristone-misoprostol administration, and three of these children have had congenital anomalies. The congenital anomalies were club foot, abnormal fingernails, and an immune disease that led to death.⁴⁷

The creator of the drug, Roussel-Uclaf and later Hoechst, was reluctant to engage in the U.S. Market because of concerns over lawsuits if birth defects or injury resulted because of Mifepristone. From the Harvard Report:

"The company's biggest worry may have been the fact that mifepristone and misoprostol have been shown to have teratologic effects. If a woman is administered both mifepristone and misoprostol and carries her pregnancy to term, her fetus is at risk. A child with birth defects is one of the most sympathetic plaintiffs."⁴⁸

More studies, culminating in consultation with the Services, should be conducted to alleviate, if possible, such concerns surrounding the usage of Mifepristone and the potential for teratological defects in endangered animals and listed habitats exposed to the drug through environmental contamination.

In fact, many studies and organizations have already found that Mifepristone and other pharmaceuticals have an adverse effect on animal and aquatic life:

⁴⁶ *The Life of the Abortion Pill in the United States* (2000 Harvard Library, Office for Scholarly Communication.) https://dash.harvard.edu/bitstream/handle/1/8852153/Hogan%2C_Julie.pdf?sequence=1&isAllowed=y

⁴⁷ *Id.*

⁴⁸ *Id.* at page 45.

- “Effects of long term antiprogesterone mifepristone (RU486) exposure on sexually dimorphic lncRNA expression and gonadal masculinization in Nile tilapia (*Oreochromis niloticus*),” [https://pubmed.ncbi.nlm.nih.gov/31491707/#:~:text=A%20long%2Dterm%20exposure%20of,and%20germline%20stem%20cell%20survival](https://pubmed.ncbi.nlm.nih.gov/31491707/#:~:text=A%20long%2Dterm%20exposure%20of,and%20germline%20stem%20cell%20survival;);
- “Drugs flushed into the environment could be cause of wildlife decline,” <https://www.theguardian.com/environment/2014/oct/13/drugs-flushed-into-the-environment-could-be-cause-of-wildlife-decline>;
- “Medicating the environment: assessing risks of pharmaceuticals to wildlife and ecosystems,” <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4213582/>;
- “For pharmaceuticals fouling wastewater and wildlife, solutions exist (commentary),” <https://news.mongabay.com/2022/01/for-pharmaceuticals-fouling-wastewater-and-wildlife-solutions-exist-commentary/>;
- “Impact of Pharmaceutical Waste on Biodiversity,” https://www.researchgate.net/publication/322127132_Impact_of_Pharmaceutical_Waste_on_Biodiversity;
- “Endocrine Disruptors,” https://www.biologicaldiversity.org/campaigns/pesticides_reduction/endocrine_disruptors/index.html;
- “Two synthetic progestins and natural progesterone are responsible for most of the progestagenic activities in municipal wastewater treatment plant effluents in the Czech and Slovak republics,” <https://www.sciencedirect.com/science/article/abs/pii/S0043135418301787>;
- “Determination of Hormone Antagonists in Waste-Water Samples by Micellar Electrokinetic Chromatography,” <https://link.springer.com/article/10.1007/s10337-018-3631-0>;
- “Detection of Pharmaceutical Residues in Surface Waters of the Eastern Cape Province,” <https://pubmed.ncbi.nlm.nih.gov/32517338/>;
- “Mapping multiple endocrine disrupting activities in Virginia rivers using effect-based assays,” <https://pubmed.ncbi.nlm.nih.gov/33592464/>;
- “Exposure to environmental endocrine disrupting compounds and men’s health,” <https://pubmed.ncbi.nlm.nih.gov/20347536/>;
- “Pharmaceuticals and Endocrine Disrupting Compounds in U.S. Drinking Water,” <https://pubs.acs.org/doi/10.1021/es801845a>;
- “Pharmaceuticals of Emerging Concern in Aquatic Systems: Chemistry, Occurrence, Effects, and Removal Methods,” <https://pubs.acs.org/doi/10.1021/acs.chemrev.8b00299>;
- “The pharmacokinetics of mifepristone in humans reveal insights into differential mechanisms of antiprogesterone action,” <https://pubmed.ncbi.nlm.nih.gov/14698071/>;
- “Impacts of endocrine disrupting chemicals on reproduction in wildlife and humans,” <https://www.sciencedirect.com/science/article/pii/S0013935121018855>;
- “Endocrine Disruptors in Domestic Animal Reproduction: A Clinical Issue?,” <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4584497/>; and
- “Endocrine Disruptors in Water and Their Effects on the Reproductive System,” <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7139484/>.

Presently the Medical Waste from Mifepristone usage is transmitted directly into the wastewater system when the patient completes the Mifepristone and associated misoprostol regimen. This is harmful to drinking water sources, groundwater sources, and any other sources of water that are touched by wastewater. This water does come into contact with endangered species and was not accounted for when the FDA approve Mifepristone for consumer use in 2000.

a. The generator of Medical Waste is responsible for disposal of that Medical Waste.

The generator of Medical Waste is responsible for disposal of human tissue or remains. This rule should be extended to the prescribers of Mifepristone as generators of Medical Waste. Consider that if a limb were amputated, one isn't sent home with it in a bag to dispose of elsewhere. The medical practitioner that began the chain of events leading to the creation of this "waste" is responsible for its proper disposal.

According to the EPA:

Medical waste is a subset of wastes generated at health care facilities, such as hospitals, physicians' offices, dental practices, blood banks, and veterinary hospitals/clinics, as well as medical research facilities and laboratories. Generally, medical waste is healthcare waste that that [sic] may be contaminated by blood, body fluids or other potentially infectious materials and is often referred to as regulated medical waste.⁴⁹

Accordingly, the physician or other medical practitioner that prescribes Mifepristone is thus the generator of Medical Waste – without their involvement, the prescription would never be issued or consumed, leading to the production of Medical Waste. The EPA notes in model guidelines that the generator of Medical Waste has responsibility for its disposal. Blood and human remains would usually be handled by incineration or a process of cleansing the material before disposal.⁵⁰

According to Waste Today Magazine, nearly all 50 states have enacted Medical Waste regulations to some extent. However, unlike state hazardous waste regulations, which are all compliant with the federal Resource Conservation and Recovery Act (RCRA) standards, state Medical Waste standards vary significantly. Some state Medical Waste rules are fashioned after the Medical Waste Tracking Act of 1988, while others bear little to no resemblance to that historical law. In most places, the state EPA equivalent is primarily responsible for developing and enforcing regulations for Medical Waste management and disposal. Although in some states, the department of health may play a leading role (e.g., Missouri and Oklahoma) or even serve as the primary regulatory agency, such as the case in Colorado. Where both agencies are involved, like in Louisiana and Missouri, typically the department of health is responsible for on-site management and the environmental agency is responsible for transportation and disposal.⁵¹

⁴⁹ <https://www.epa.gov/rcra/medical-waste>

⁵⁰ https://www.epa.gov/sites/default/files/2016-02/documents/model_guidelines_for_state_medical_waste_management.pdf

⁵¹ <https://www.wastetodaymagazine.com/article/medical-waste-regulation-processing/>

There is no generalized nationwide direction from states or the federal government for the proper disposal of fetal remains, a problem that plagues the entirety of the abortion industry. The FDA, through a modification of the Mifepristone REMS, can begin to alleviate this problem and establish a national disposal standard. Most states' laws are too broad in this context to truly encapsulate what is necessary for the safe disposition of fetal remains or, by extension, the chemical remains from Mifepristone.

CONCLUSION

This Petition requests that the FDA conduct the appropriate consultation under Section 7 of the Endangered Species Act with the United States Fish and Wildlife Service and National Marine Fisheries Service in light of the unknown affect that Mifepristone could have on all listed endangered or threatened species or designated critical habitats in the FDA's approval jurisdiction.

The Endangered Species Act requires federal agencies to consult with the Services to ensure that the actions they fund, authorize, permit, or otherwise carry out will not jeopardize the continued existence of any listed species or adversely modify designed critical habitats. When approving Mifepristone for human consumption, the FDA did not do this.

The purpose of the Endangered Species Act is to provide a means to conserve the ecosystems upon which endangered and threatened species depend and provide a program for the conservation of such species. The Section 7 consultation requirements apply to all federal agency actions.

Because FDA did not perform the proper consultation under the Act, it is unknowable the impact Mifepristone and its by-products may have on the nation's waterways and ecosystems, and more specifically the impact the same has had and will have on endangered species or listed habitats. The approval of Mifepristone should be halted to allow for a full investigation into its harms to humans, the environment, and endangered species, as required by law.

C. ENVIRONMENTAL IMPACT

Petitioner is categorically excluded from conducting an environmental impact statement under 21 C.F.R. § 25.30, 25.31, 25.32, 25.33, or § 25.34 or an environmental assessment under 21 C.F.R. § 25.40.

D. ECONOMIC IMPACT

Petitioner will submit information upon request of the Commissioner following review of this petition.

E. CERTIFICATION

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

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Cedarville Students for Life
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Advocates for Life (Cleveland State University)
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New York University Catholic Center
Students for Life of Delta State University
DePaul College Republicans
East Career & Tech Academy Students for Life
East Tennessee State University Students for Life
Students for Life Eastern Washington University
Evansville Christian School Students for Life
Alive with New Hope
Fairmont State University Students for Life
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Students Cherishing Life (Hope College)
Huntington University Students for Life
IC Imagine Students for Life
Students for Life at Illinois State University
Students for Life at Indiana University
Iowa State Students for Life
College Republicans at Indiana University Purdue University Indianapolis
Jones College Preparatory High School Students for Life
Judson Bike Shop (Judson University)
Kalida High School Students for Life
Kent State Flashes for Life
Protect Life Club (Lake Superior State University)
Liberty University Students for Life
Lorain County Community College Students for Life
Duhawks for Life (Loras College)
Lumen Christi Catholic School Students for Life
Teens for Life (Lutheran High School of St. Charles)
Lancers for Life (Lutheran High School South)
Indiana University Robert H. McKinney School of Law Students for Life
Miami University Students for Life
Middle Tennessee State University Students for Life
Mississippi College Students for Life
Pro-Life Mississippi State University
Bears For Life (Missouri State University)
Rolla Students for Life (Missouri University of Science and Technology)
Montclair State University Students for Life
Gianna Project Students for Life of America (Northpoint Homeschool)
Northwest Students for Life (Northwest Missouri State University)
PLGVoices (Northwestern Health Sciences University)
OCA Pro-Life
Bobcats for Life (Ohio University)
Ottawa Glandorf Students for Life
Ozark Catholic
Palm Beach Atlantic University Students for Life
Potomac Falls High School Students for Life
Students for Life of Purdue University Fort Wayne
Regent University Students for Life

Richmond Students for Life
Rockhurst Respect Life
CSA (Rutgers University)
Imago Dei Students for Life
St. Louis University Students for Life
Belles for Life (St. Mary's College)
Saint Vincent College Respect Life Club
Bearkats For Life (Sam Houston State University)
Shippensburg Students for Life
Students for Life Southeast Missouri State University
Students for Life Southeastern University
Raiders 4 Life (Southridge Highschool)
Mavs for Life Southside High School
St. Francis High School Students for Life
Stone Bridge Students for Life (Stone Bridge High School)
Surry Students for Life (Surry Community College)
Tarleton Students for Life (Tarleton State University)
Temple University Students for Life
Buckeyes for Life (The Ohio State University)
Students for Life at the University of Tennessee at Martin
Students for Life at the University of Texas at El Paso
Thomas More University Saints for Life
Students for Life of Traverse City West Senior High School
Students for Life at Truman State University
Students For Life at Tuscarora High School
University of Akron Students for Life
Students for Life at University of Arizona
University of Chicago Students for Life
University of Cincinnati Students for Life
Flyers for Life (University of Dayton)
University of Detroit Mercy Protect Life Group
Student for Life at University of Florida
We Dignify (University of Illinois Urbana-Champaign)
Pro-Life Wildcats (University of Kentucky)
Louisville Students for Life
Cru for Life (University of Mary Hardin-Baylor)
Mizzou Students for Life (University of Missouri)
Students for Life at University of Missouri – St. Louis
Students for Life at University of Nevada – Reno
University of Northern Iowa Students for Life
University of South Florida Students for Life
Celts for Life (University of St. Thomas)
University of Tennessee – Knoxville Vols for Life
Toledo Students for Life
Students for Life at University of West Florida
Students for Life at the University of Nevada, Las Vegas School of Dental Medicine

Students for Life at Utah Valley University
Students for Life at the University of Texas San Antonio
Students for Life of America at Virginia Commonwealth University
Students for Life at Virginia Tech
Washington and Lee University Students for Life
Students for Life at Watkins Mill High School
Mountaineers for Life (West Virginia University)
Western Kentucky University Students for Life
Woodgrove Students for Life (Woodgrove High School)
Students for Life at West Virginia University Institute of Technology
Cowboys for Life (Wyoming Catholic College)
Xavier Students for Life (Xavier University)
Abilene Christian University for Life
Raiders Defending Life (Texas Tech University)
Rice for Life (Rice University)

Exhibit No.	Exhibit Name
A	Supplement Approval for NDA 020687/S-014 (June 8, 2011), https://perma.cc/JJJ9-NYKQ
B	Supplement Approval for NDA 020687/S-022 (Apr. 11, 2019), https://perma.cc/WU6K-GFLF
C	REMS Modification Rationale Review (Dec. 16, 2021), https://perma.cc/P38G-3NU5 (beginning at page 41 of the PDF)
D	P. Cavazzoni to D. Harrison, <i>et al.</i> (Dec. 16, 2021), https://www.regulations.gov/document/FDA-2019-P-1534-0016 (last visited June 3, 2023)
E	REMS Modification Notification for NDA 020687 (Dec. 16, 2021)
F	REMS Modification Notification for ANDA 091178 (Dec. 16, 2021)
G	CDER, Summary Review (Application Number: 020687Orig1s025) (Jan. 3, 2023), https://perma.cc/P38G-3NU5 (beginning at page 1 of the PDF)
H	CDER, Risk Assessment and Risk Mitigation Review(s) (Application Number: 202107Orig1s000) (Jan. 27, 2012), https://perma.cc/DZ3M-MX93
I	<i>Guidance for Industry: REMS: FDA's Application of Statutory Factors in Determining When a REMS Is Necessary</i> (Apr. 2019), https://perma.cc/X7V4-9MZJ
J	A. Shah, M.D., to H. Balderas (May 19, 2020)
K	Supplement Approval for NDA020687/S-025 (Jan. 3, 2023), https://perma.cc/5FTY-SY25
L	Citizen Petition from Students for Life of America (Apr. 19, 2023), https://www.regulations.gov/document/FDA-2023-P-1528-0001 (last visited June 3, 2023)

I swear under penalty of perjury that the foregoing is true and correct.

Executed on June 5, 2023.

/s/ Noah T. Katzen
NOAH T. KATZEN